April 18, 2006

Roger Citron, RPh
Mountain Department of Public
Health & Human Services
1400 Broadway
Helena, MT 59602-2951

Dear Mr. Citron:

In response to the Montana Medicaid Drug Use Review Board/Formulary Committee Meeting, we are providing you with a dossier that is consistent with the Academy of Managed Care Pharmacy's (AMCP) format for pharmaceutical manufacturers for your consideration at the Preferred Drug List review beginning May 3, 2006. Additionally, at your request, we are providing the Avelox® (moxifloxacin hydrochloride) Tablets and Avelox® I.V. (moxifloxacin hydrochloride in sodium chloride injection) AMCP Managed Care Dossier in an electronic format (CD) to facilitate your review process.*

The purpose of this formulary submission dossier is to present the clinical and economic rationale to support the use of moxifloxacin (Avelox) within your health plan for the treatment of adults (≥ 18 years of age) with infections caused by susceptible strains of the designated microorganisms in the following conditions: Acute Bacterial Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, Community Acquired Pneumonia (including multi-drug resistant strains*), Uncomplicated and Complicated Skin and Skin Structure Infections and Complicated Intra-Abdominal Infections. Please refer to the enclosed Avelox Product Information Sheet for a complete listing of susceptible strains of the designated microorganisms for each of the indications listed above.

* MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (Penicillin-resistant *S. pneumoniae)*, and are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2 µg/mL), 2 nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

* This information is provided as a professional service in response to your unsolicited inquiry. It is intended to provide you with a fair, balanced, and objective review of the available scientific literature and/or data that you requested. This response is not intended to offer recommendations for use of this or any product inconsistent with approved product labeling. Please refer to the package insert for full prescribing information.

Structure of This Dossier

1. Section 1 provides product information for Avelox®, including the FDA approved indications, pharmacology, pharmacokinetics, dosage forms as well as place in therapy.

2. Section 2 provides a summary of the supporting clinical and economic information for Avelox®, based on results from published and unpublished efficacy and safety studies.

3. Section 3 provides information regarding the expected impact and cost-effectiveness of Avelox® therapy to help estimate the potential plan-specific budget impact of including Avelox® on the formulary. This is merely an economic model and does not constitute any reimbursement advice.

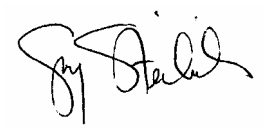
If you have any questions on the clinical portion of the dossier, please contact Global Drug Information Services at (800) 526-4099.

The following person may be contacted to provide additional information regarding submission materials:

Aimee M Redhair
Regional Account Manager
Schering Plough US Managed Markets
Office: 720-283-4692
Cell: 303-241-7501
aimee.redhair@spcorp.com

Based on the findings, Schering believes Avelox should be placed on the preferred drug list of contract drugs without restrictions.

Sincerely,



Gay Steinbrick, Pharm.D.
Sr. Director, Global Drug Information Services

2006-18189
Enclosures:
CD of Avelox AMCP Dossier
Avelox Product Information sheet
References
Formulary Submission Checklist
cc: Aimee M Redhair

Executive Summary

In response to your unsolicited request, we are providing this document, the purpose of which is to supply information on the usage of Avelox® (moxifloxacin hydrochloride) Tablets and Avelox® (moxifloxacin hydrochloride in sodium chloride injection) IV Injection to assist you in your formulary decision-making process.

- Avelox® is a broad-spectrum fluoroquinolone that is FDA approved for the following indications:

Indications:	**Caused by:**
Acute bacterial exacerbation of chronic bronchitis (ABECB)	*Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Staphylococcus aureus,* or *Moraxella catarrhalis*
Acute bacterial sinusitis (ABS)	*Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis*
Community-acquired pneumonia (CAP)	*Streptococcus pneumoniae (*including multi-drug resistant strains**), Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae,* or *Chlamydia pneumoniae*
Uncomplicated skin and skin structure infections (uSSSI)	*Staphylococcus aureus* or *Streptococcus pyogenes*
Complicated skin and skin structure infections (cSSSI)	methicillin susceptible *Staphylcoccus aureus, Escherichia coli, Klebsiella pneumoniae* or *Enterobacter cloacae*

*Multi-drug resistant *Streptococcus pneumoniae* (MDRSP) includes isolates previously known as PRSP (penicillin-resistant *S. pneumoniae*) and are strains resistant to two or more of the following antibiotics: penicillin (MIC = 2 µg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

- The clinical efficacy of Avelox® has been demonstrated in the treatment of infection due to gram-positive and gram-negative organisms, including multi-drug resistant strains of *Streptococcus pneumoniae* and atypical pathogens commonly identified in community acquired pneumonia patients.

- Avelox® offers convenient once daily dosing in a single 400 mg strength that does not require dosage adjustment upon transitioning from an intravenous (IV) to an oral (PO) route of administration.

- No dosage adjustment is required for Avelox® in patients with renal or hepatic (Child Pugh Classes A and B)♣ impairment.

- Avelox® is widely distributed throughout the body, with tissue concentrations often exceeding plasma concentrations. Clinical pharmacokinetic studies have shown that Avelox® attains high concentrations in the target tissues quickly, such as the alveolar macrophages and epithelial lining fluid (Capitano et al, 2004), in the sinus tissues (Gehanno et al, 2002), as well as in the inflammatory

♣ The pharmacokinetics of moxifloxacin in severe hepatic insufficiency (Child Pugh Class C) have not been studied.

fluids (Wise et al, 1999), and maintains concentrations above MIC_{90} values for common pathogens associated with respiratory tract infections.

- Resistance to β-lactams and macrolides is an increasing concern among common respiratory pathogens as case reports of Levaquin®Ψ (levofloxacin) resistance developing within days of the initiation of treatment (Low et al, 2004) have been reported. Avelox® is bacteriocidal and has a dual mechanism of action, attributed to inhibition of both bacterial DNA gyrase and topoisomerase IV (Avelox PI). Avelox® has shown that *in vitro** resistance develops slowly via multiple-step mutations and has a decreased susceptibility to bacterial efflux mechanisms due to Avelox's® bulky side chain at the C-7 position. In an *in vitro** study, Avelox® showed a lower propensity to select resistant mutants of *S. pneumoniae* after repeated overnight exposures to suboptimal concentrations compared with Levaquin®Ψ (levofloxacin) and Floxin®Ψ (ofloxacin) (Scheld, 2003).

- Studies have shown that Avelox® has proven superior efficacy in the treatment of CAP (Data on File, Study 10872/MRR-00140), ABS (Siegert et al, 2000; Data on File, Schering Corporation), and ABECB (Wilson et al, 2004) when compared with the following: levofloxacin, cefuroxime axetil, amoxicillin, or clarithromycin.

- Overall, clinical studies have shown that Avelox's® safety profile is comparable to it comparators, including β-lactams, advanced generation macrolides, and other fluoroquinolones.

- Several large, prospective, comparative clinical trials were conducted that evaluated the cardiac safety of Avelox® to its comparators (including alatrofloxacin/trovafloxacin, levofloxacin, co-amoxiclav) (File et al, 2001; Finch et al, 2002; Data on File, Study 10872/MRR-00140). In these studies, the incidence of cardiac events, including effect on the QT interval, was not found to be statistically significant between treatment groups.ϒ

- Avelox® is NOT contraindicated in patients with an allergy to penicillin.

- A retrospective analysis study on the use of Avelox® and its effect on glucose homeostasis found that the incidence of hypo- and hyper-glycemia was similar between Avelox® and its comparators (broad spectrum penicillins [amoxicillin, Augmentin®Ω {amoxicillin/clavulanic acid}], cephalosporins [Ceftin®Ω {cefuroxime axetil}], macrolides [Zithromax®♦ {azithromycin}, Biaxin®♣ {clarithromycin}], doxycycline, and other fluoroquinolones [Trovan®♦ {trovafloxacin}, Levaquin®Ψ {levofloxacin}]) (Gavin et al, 2004).

- The effect of UVA and UVB light on healthy patients taking Avelox® was not significant (Man et al, 1999).

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* The clinical relevance of *in vitro* data is not known.

ϒ **Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g. amiodar one, sotalol) antiarrhythmic agents, due to the lack of clinical experience with the drug in these patient populations.** (Please see the Avelox Product Information Sheet for complete Warnings, Precautions, and Adverse Events).

Community Acquired Pneumonia (CAP)

- Avelox® has proven efficacy (clinical and bacteriological) in the treatment of CAP, in healthy patients, patients who require hospitalization, as well as elderly patients, and a safety profile similar to it's comparators in clinical trials.

- In the CAPRIE study, there was no significant difference between moxifloxacin and levofloxacin with respect to cardiac safety, the primary endpoint of the study (Data on File, Study 10872/MRR-00140).

- In a prospective, randomized, comparative clinical trial conducted in elderly patients, significantly more patients treated with Avelox® had an assessment of clinical recovery (resolution or improvement) by day 3-5 than Levaquin®Ψ (levofloxacin) treated patients (97.9% vs 90.0%, 95% CI, 1.7-14.1; p=0.01) (Data on File, Study 10872/MRR-00140).

- Avelox® has proven efficacy in treating patients with severe CAP. In patients who require initial IV therapy, a significantly faster IV to oral transition by day 5 was observed in patients receiving Avelox versus the comparator (73% vs 60%, respectively, p<0.01) (includes Augmentin®Ω [amoxicillin/clavulanate), Biaxin®♣ [clarithromycin], Trovan®♦ [alatrofloxacin, trovafloxacin], Levaquin®Ψ [levofloxacin]) (Lode et al, 2003).

- In comparative clinical trials, Avelox® has shown to be as effective as standard treatment with an advanced macrolide either alone or with a β-lactam (Katz et al, 2004; File, 2001; Hoeffken et al, 2001; Fogarty et al, 1999) or more effective than an IV/PO regimen of Augmentin®Ω (co-amoxiclav) with or without Biaxin®♣ (clarithromycin) (Finch et al, 2002).

Acute Bacterial Sinusitis (ABS)

- In comparative clinical trials, Avelox® has proven to be as effective as its comparators, including Ceftin®Ω (cefuroxime axetil), Ketek®β (telithromycin), Trovan®♦ (trovafloxacin), and Augmentin®Ω (amoxicillin clavulanate), for the treatment of acute bacterial sinusistis, in a convenient, once daily dosing regimen.

- When compared to Levaquin®Ψ (levofloxacin), a retrospective, database analysis study showed that Avelox® treated patients had a significantly lower probability of sinusitis recurrence (36%) (p=0.0062) and a significantly lower treatment failure rate (10.4% vs 14.0%, Avelox® and Levaquin®Ψ (levofloxacin), respectively) (p=0.003) (Data on File).

- In a prospective, comparative clinical trial, a significantly greater number of patients treated with Avelox® 400 mg for 10 days, reported feeling better by day 3 than the comparator (Augmentin®Ω [amoxicillin clavulanate] 875 mg twice daily) treated patients (24% vs 14%, respectively, p<0.02) (Rakkar et al, 2001).

- A prospective, non-comparative study was conducted in patients with acute maxillary sinusitis after first line treatment failure and acute sinusitis with high risk of complications where Avelox® was administered for 7 days*. In this patient population, the reported clinical resolution rates were above

* For the treatment of acute bacterial sinusitis, the recommended dosing regimen of moxifloxacin is 400 mg for 10 days.

90% and improvement in their condition by day 3-4 of treatment was reported by 94.9% of patients. Bacteriological success was seen in 97.2% of patients with maxillary sinusitis after first-line treatment failure and 95.2% of patients with sinusitis and risk of complications (Gehanno et al, 2003).

Acute Exacerbation of Chronic Bronchitis (AECB)

- Avelox® proved to be as effective as comparator treatment regimens (included amoxicillin, Biaxin®♣ [clarithromycin] or Ceftin®Ω [cefuroxime axetil]) for the treatment of acute exacerbation of chronic bronchitis (Wilson et al, 2001).

- In the MOSAIC trial, Avelox® treated patients showed a statistically significant lower mean time to the next acute exacerbation of acute bronchitis than the comparator treated patients (amoxicillin, Biaxin®♣ (clarithromycin), or Ceftin®Ω (cefuroxime axetil)) (p=0.03) (Wilson et al, 2004).

- Avelox® treated patients also had a signficantly lower frequency of additional antibiotic therapy in the per protocol and intent to treat populations (p=0.045 and p=0.006, respectively) and a higher proportion of Avelox® treated patients received no concomitant steroid therapy or had no change in their existing steroid regimen (p=0.03 in the intent to treat population) (Wilson et al, 2004).

- In a multi-center, observational study, the mean time to recovery was significantly shorter, statistically, in Avelox® treated patients (4.6 ± 3.3 days) versus the comparator (5.8 ± 4.6 days) (p<0.01) (Miravitlles et al, 2004).

Uncomplicated and Complicated Skin and Skin Structure Infections

- For the treatment of uncomplicated skin and skin structure infections, Avelox® has proven to be as effective, clinically and bacteriologically, as cephalexin, with a comparable safety profile (Parish et al, 2000).

- Avelox® received FDA approval (June, 2005) for the treatment of complicated skin and skin structure infections due to methicillin susceptible *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae*, or *Enterobacter cloaca*. Clinical studies have proven that IV/PO Avelox® is as effective, clinically and bacteriologically, as Zosyn®a (IV piperacillin/tazobactam) or Augmentin®Ω (IV/PO amoxicillin clavulanate)* (Data on File, Study 10279/MRR-00133; Data on File, Study 100273/MRR-00082).

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* IV amoxicillin clavulanate is not FDA approved.

Ω Augmentin® and Ceftin® are a registered trademark of Glaxo SmithKline.

Ψ Levaquin® and Floxin® are registered trademarks of Ortho-McNeil Pharmaceutical, Inc.

♣ Biaxin® is a registered trademark of Abbot Laboratories.

a Zosyn® is a registered trademark of Wyeth Pharmaceuticals, Inc.

♦ Zithromax® and Trovan® are registered trademarks of Pfizer, Inc.

β Ketek® is a registered trademark of Aventis Pharmaceuticals, Inc.

Section 1. Product Information

1.1 Product Description – Moxifloxacin Hydrochloride (Avelox®)

1.1.a Name

Moxifloxacin hydrochloride (Avelox®): Antibacterial Agent

1.1.b Dosage Forms, Strengths, and Package Size

Avelox® tablets are available as oblong, red film-coated tablets containing 400 mg of moxifloxacin supplied in bottles of 30, and unit-dose packs of 5 and 50 tablets. Avelox® IV is available in ready-to-use 250-mL, latex-free, flexible bags containing 400 mg of moxifloxacin in a 0.8% sodium chloride solution.

1.1.c National Drug Code (NDC)

Avelox® 400-mg tablets:

Bottles of 30:	0085-1733-01
Unit Dose Pack of 50:	0085-1733-02
ABC Pack of 5:	0085-1733-03

Avelox® 400-mg IV:

250-mL flexible container	0085-1737-01

1.1.d Copy of Current Product Labeling

See attached

1.1.e AWP/WAC Cost

N/A

1.1.f American Hospital Formulary Service (AHFS) Drug Classification

Quinolones 8:22

1.1.g FDA-Approved Indications

Moxifloxacin tablets and intravenous solution are indicated for the treatment of adults (= 18 years of age) with infections caused by susceptible strains of the designated microorganisms in the conditions listed:

Indications:	**Caused by:**
Acute bacterial exacerbation of chronic bronchitis (ABECB)	*Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Staphylococcus aureus,* or *Moraxella catarrhalis*
Acute bacterial sinusitis (ABS)	*Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis*
Community-acquired pneumonia (CAP)	*Streptococcus pneumoniae (*including multi-drug resistant strains**), Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*
Uncomplicated skin and skin structure infections (uSSSI)	*Staphylococcus aureus* or *Streptococcus pyogenes*
Complicated skin and skin structure infections (cSSSI)	methicillin susceptible *Staphylcoccus aureus, Escherichia coli, Klebsiella pneumoniae* or *Enterobacter cloacae*

*Multi-drug resistant *Streptococcus pneumoniae* (MDRSP) includes isolates previously known as PRSP (penicillin-resistant *S. pneumoniae*) and are strains resistant to two or more of the following antibiotics: penicillin (MIC = 2 µg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

1.1.h Microbiology

Moxifloxacin is a synthetic fluoroquinolone with *in vitro*[*] activity against a wide range of Gram-positive and Gram-negative microorganisms. The bactericidal action of moxifloxacin results from the inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV required for DNA replication, transcription, repair, and recombination.

Fluoroquinolones, including moxifloxacin, differ in chemical structure and mechanism of action from those of macrolides, β-lactams, aminoglycosides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antimicrobials. *In vitro* resistance to moxifloxacin develops slowly via multiple-step mutations. Cross-resistance has been observed between moxifloxacin and other fluoroquinolones against Gram-negative bacteria. Gram-positive bacteria resistant to other fluoroquinolones may, however, still be susceptible to moxifloxacin.

Clinical studies and *in vitro* data indicate that moxifloxacin is active against most strains of *Staphylococcus aureus* (methicillin-susceptible strains only), *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]*), *Streptococcus pyogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, and Mycoplasma pneumoniae.*

*MDRSP includes isolates previously known as PRSP and are strains resistant to two or more of the following antibiotics: penicillin (MIC = 2 µg/mL), 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Moxifloxacin also exhibits an *in vitro* minimum inhibitory concentration (MIC) of 2 µg/mL or less against most (= 90%) strains of *Staphylococcus epidermidis* (methicillin-susceptible strains only), *Streptococcus* viridans group, *Streptococcus agalactiae*, *Peptostreptococcus* species, *Citrobacter freundii, Klebsiella oxytoca, Legionella pneumophila, Proteus mirabilis, Fusobacterium* species, and *Prevotella* species. However, it should be noted that the effectiveness and safety of moxifloxacin in treating clinical infections caused by these organisms have not been evaluated.

Appropriate culture and susceptibility tests should be performed before treatment with moxifloxacin to isolate and identify the organism causing infection and to determine susceptibility to moxifloxacin. Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations to provide estimates of the susceptibility of bacteria to antimicrobial compounds. MICs for moxifloxacin should be interpreted according to specific criteria listed in Avelox® product labeling.

1.1.i Pharmacokinetics/Pharmacodynamics

Absorption:

When administered as an oral tablet, moxifloxacin is well absorbed from the GI tract with an absolute bioavailability of approximately 90%. Co-administration with a high fat meal does not affect the absorption of moxifloxacin. Consumption of 1 cup of yogurt with moxifloxacin does not significantly affect the rate or extent of systemic absorption.

[*] The clinical relevance of *in vitro* data is not known.

Maximum plasma concentrations are attained within 1 to 3 hours following oral dosing. The mean (± SD) C_{max} and AUC values at steady state following a multiple dose 400-mg daily oral dosing regimen are 4.5 ± 0.5 µg/mL and 48 ± 2.7 µg·h/mL, respectively, in young healthy males and females. The mean (± SD) C_{max} and AUC values at steady state following a 400-mg daily intravenous dosing regimen are 4.2 ± 0.8 µg/mL and 38.0 ± 4.7 µg•h/mL, respectively, in young healthy males. Plasma concentrations increase proportionately with increasing dose up to 1200 mg orally per day.

Distribution:
Moxifloxacin is approximately 50% bound to serum proteins, independent of drug concentrations. The volume of distribution of moxifloxacin ranges from 1.7 to 2.7 L/kg. The drug is widely distributed throughout the body and has been detected in saliva, nasal and bronchial secretions, mucosa of the sinuses, skin blister fluid, and subcutaneous tissue, and skeletal muscle following oral or intravenous administration of 400 mg. Tissue concentrations often exceed plasma concentrations. Tissue concentrations measured 3 hours after a single oral dose of 400 mg of moxifloxacin in the alveolar macrophages, bronchial mucosa, and epithelial lining fluid were 61.8 ± 27.3 µg/g, 5.5 ± 1.3 µg/g, and 24.4 ± 14.7 µg/g, respectively. Tissue concentrations measured after 5 days of daily dosing with 400 mg of moxifloxacin in the maxillary sinus mucosa, anterior ethmoid mucosa, and nasal polyps were 7.6 ± 1.7 µg/g, 8.8 ± 4.3 µg/g, and 9.8 ± 4.5 µg/g, respectively. Tissue concentrations measured 3 hours after a single oral dose of 400 mg of moxifloxacin in blister fluid, subcutaneous tissue and skeletal muscle were 2.6 ± 0.05, 0.9 ± 0.3,* and 0.9 ± 0.2,* respectively. The rates of elimination of moxifloxacin from the tissues generally parallel the elimination from plasma.

Metabolism:
Approximately 52% of an oral or intravenous dose of moxifloxacin is metabolized via glucuronide and sulfate conjugation. The hepatic cytochrome P450 enzyme system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. The sulfate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the feces. Approximately 14% of an oral or intravenous dose is converted to the glucuronide conjugate (M2), which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% of those of the parent drug, while plasma concentrations of M1 are generally less than 10% of those of moxifloxacin.

Excretion:
Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~ 25% in feces). Approximately 96% ± 4 % of an oral dose is excreted as either unchanged drug for known metabolites. The mean (± SD) apparent total body clearance and renal clearance are 12 ± 2.0 L/h and 2.6 ± 0.5 L/h, respectively.

* Reflects only non-protein bound drug

Special Populations:
Geriatric:
No age-related differences in pharmacokinetic parameters, including the extent of total systemic exposure and elimination half-life, were noted during pharmacokinetic studies or clinical trials. No dosage adjustments are necessary based on age.

Pediatric:
The pharmacokinetics of moxifloxacin in pediatric subjects has not been studied.

Renal Insufficiency:
The pharmacokinetic parameters of moxifloxacin are not significantly altered by mild, moderate, severe, or end-stage renal disease. No dosage adjustment is necessary in patients with renal impairment, including those patients requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Hepatic Dysfunction:
No dosage adjustment is recommended for patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic insufficiency. The pharmacokinetics of moxifloxacin in patients with severe (Child Pugh Class C) hepatic insufficiency has not been studied.

Gender:
Dosage adjustments based on gender are not necessary. A 400-mg moxifloxacin single-dose study was conducted in 18 young males and females. The comparison of moxifloxacin pharmacokinetics showed no differences in AUC or C_{max} due to gender. There were no significant differences in moxifloxacin pharmacokinetics in male and female subjects when differences in body weight were taken into consideration.

Ethnicity:
No pharmacokinetic differences based on ethnic origin are noted. Steady state moxifloxacin pharmacokinetics in male Japanese subjects were similar to those determined in Caucasians, with a mean C_{max} of 4.1 µg/mL, and AUC_{24} of 47 µg•h/mL, and an elimination half-life of 14 hours, following 400 mg orally daily.

1.1.j Contraindications
Moxifloxacin is contraindicated in persons with a history of hypersensitivity to moxifloxacin or any member of the quinolone class of antimicrobial agents.

1.1.k Warnings/Precautions
The safety and efficacy of moxifloxacin in pediatric patients, adolescents (< 18 years of age), pregnant women, and lactating women have not been established.

Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving Class IA (eg, quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents, due to the lack of clinical experience with the drug in these patient populations.

Pharmacokinetic studies between moxifloxacin and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of moxifloxacin and these drugs cannot be excluded, therefore caution should be exercised when moxifloxacin is given concurrently with these drugs. In premarketing clinical trials, the rate of cardiovascular adverse events was similar in 798 moxifloxacin and 702 comparator treated patients who received concomitant therapy with drugs known to prolong the QTc interval.

Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT prolongation may increase with increasing concentrations of the drug or increasing rates of infusion of the intravenous formulation. Therefore the recommended dose or infusion rate should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes.

As with related quinolone-class drugs, moxifloxacin has been shown in animal studies to cause arthropathy and/or erosions of cartilage of weight-bearing joints in immature dogs.

Convulsions have been reported in patients receiving quinolones. Quinolones may also cause central nervous system (CNS) events including dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in the patients receiving moxifloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, moxifloxacin should be used with caution in patients with known or suspected CNS disorders (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold.

Moxifloxacin is contraindicated in persons with a history of hypersensitivity to moxifloxacin or any member of the quinolone class of antimicrobial agents. Anaphylactic reactions, some following the first dose, have been reported in patients receiving quinolone therapy including moxifloxacin.

Serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have been reported in patients receiving therapy with all antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: rash, fever, eosinophilia, jaundice, and hepatic necrosis.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, and it may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Achilles and other tendon ruptures that require surgical repair or resulted in prolong disability have been reported in patients receiving quinolones. Post-marketing surveillance reports indicate the risk may be increased in those receiving corticosteroids or especially in the elderly. Moxifloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

Peripheral neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones.

Pregnancy: Teratogenic Effects. Pregnancy Category C: Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day or 0.24 times

the maximum recommended human dose based on systemic exposure (AUC), but decreased fetal body weights and slightly delayed fetal skeletal development (indicative of fetotoxicity) were observed. Intravenous administration of 80 mg/kg/day (approximately 2 times the maximum recommended human dose based on body surface area (mg/m^2)) to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day. Intravenous administration of 20 mg/kg/day (approximately equal to the maximum recommended human oral dose based upon systemic exposure) to pregnant rabbits during organogenesis resulted in decreased fetal body weights and delayed fetal skeletal ossification. When rib and vertebral malformations were combined, there was an increased fetal and litter incidence of these effects. Signs of maternal toxicity in rabbits at this dose included mortality, abortions, marked reduction of food consumption, decreased water intake, body weight loss and hypoactivity. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (2.5 times the maximum recommended human dose based upon systemic exposure). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. In an oral pre- and postnatal development study conducted in rats, effects observed at 500 mg/kg/day included slight increases in duration of pregnancy and prenatal loss, reduced pup birth weight and decreased neonatal survival. Treatment-related maternal mortality occurred during gestation at 500 mg/kg/day in this study.

Since there are no adequate or well-controlled studies in pregnant women, moxifloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

1.1.l Adverse Effects

During worldwide clinical efficacy trials, over 8,600 patients received treatment with oral or intravenous moxifloxacin (of whom 8,000 patients received the 400-mg dose). Most adverse events reported during moxifloxacin clinical trials were described as mild to moderate in severity intensity, and required no treatment. Moxifloxacin was discontinued due to adverse reactions judged by investigators to be at least possibly drug related in 2.9% of orally treated patients and 4.6% of sequentially (intravenous followed by oral) treated patients. The latter studies were conducted in community acquired pneumonia and complicated skin and skin structure infections with, in general, a sicker population compared to the tablet studies.

Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in ≥ 2% of moxifloxacin-treated patients included nausea (6%), diarrhea (5%), and dizziness (2%).

Additional clinically relevant uncommon events, judged by investigators to be at least possibly drug-related, that occurred in = 0.1% and less than 2% of moxifloxacin-treated patients included:

BODY AS A WHOLE - abdominal pain, headache, asthenia, injection site reaction (including phlebitis), moniliasis, pain, allergic reaction
CARDIOVASCULAR - tachycardia, palpitation, vasodilation, QT interval prolonged, hypertension
NERVOUS SYSTEM - insomnia, nervousness, vertigo, somnolence, anxiety tremor
DIGESTIVE - vomiting, abnormal liver function test, dyspepsia, dry mouth, flatulence, oral moniliasis, constipation, GGTP increased, anorexia, stomatitis, glossitis
HEMIC AND LYMPHATIC - leukopenia, eosinophilia, prothrombin decrease (prothrombin time prolonged/International Normalized Ratio (INR) increased), thrombocythemia, anemia
METABOLIC AND NUTRITIONAL - lactic dehydrogenase increased, amylase increased
MUSCULOSKELETAL - arthralgia, myalgia

SKIN/APPENDAGES - rash (maculopapular, purpuric, pustular), pruritis, sweating, urticaria
SPECIAL SENSES - taste perversion
UROGENITAL - vaginal moniliasis, vaginitis and kidney function abnormal.

Additional clinically relevant rare events, judged by investigators to be at least possibly drug-related, that occurred in < 0.1% of moxifloxacin-treated patients were:

- abnormal dreams
- abnormal vision
- agitation
- amblyopia
- amnesia
- aphasia
- arthritis
- asthma
- atrial fibrillation
- back pain
- chest pain
- confusion
- convulsions
- depersonalization
- depression
- dysphagia
- dyspnea
- ECG abnormal
- emotional lability
- face edema
- gastritis
- gastrointestinal disorder
- hallucinations
- hyperglycemia
- hyperlipidemia
- hypertonia
- hyperuricemia
- hypesthesia
- hypotension
- incoordination
- jaundice (predominantly cholestatic)
- lab test abnormal (not specified)
- leg pain
- malaise
- paraesthesia
- parosmia
- pelvic pain
- peripheral edema
- pseudomembranous colitis
- prothrombin increase (prothrombin time decreased/International Normalized Ratio (INR) decreased)
- sleep disorders
- speech disorders
- supraventricular tachycardia
- syncope
- taste loss
- tendon disorder
- thinking abnormal
- thrombocytopenia
- thromboplastin decrease
- tinnitus
- tongue discoloration
- ventricular tachycardia

Additional adverse effects have been reported from worldwide post-marketing experience with moxifloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events, some of them life threatening, include anaphylactic reaction, anaphylactic shock, angioedema (including laryngeal edema), hepatitis (predominantly cholestatic), psychotic reaction, Stevens-Johnson syndrome, tendon rupture, and ventricular tachyarrhythmias (including in very rare cases cardiac arrest and torsades de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions).

Changes in laboratory parameters, without regard to drug relationship, which are not listed above and which occurred in = 2% of patients and at an incidence greater than in controls included: increases in MCH, neutrophils, WBCs, PT ratio, ionized calcium, chloride, albumin, globulin, bilirubin; decreases in hemoglobin, RBCs, neutrophils, eosinophils, basophils, PT ratio, glucose, pO_2, bilirubin and amylase. It cannot be determined if any of the above laboratory abnormalities were caused by the drug or the underlying condition being treated.

1.1.m Drug Interactions

Antacids, Sucralfate, Metal Cations, Multivitamins: Quinolones form chelates with alkaline earth and transition metal cations. Oral administration of quinolones with antacids containing magnesium or aluminum, or other products containing metal cations such as sucralfate and didanosine

(VIDEX®τ) chewable/buffered tablets or pediatric powder for oral solution may substantially interfere with the absorption of quinolones, resulting in systemic concentrations considerably lower than desired. Therefore, moxifloxacin should be taken at least 4 hours before or 8 hours after these agents.

No clinically significant drug-drug interactions between itraconazole, theophylline, warfarin, digoxin, atenolol, oral contraceptives, or glyburide have been identified with moxifloxacin. Additionally, itraconazole, theophylline, warfarin, digoxin, probenecid, morphine, ranitidine, and calcium did not significantly affect the pharmacokinetics of moxifloxacin. Moxifloxacin is unlikely to affect the metabolic clearance of other drugs metabolized by the cytochrome P450 CYP3A4, CYP2C9, CYP2D6, CYP2C19, or CYP1A2 enzyme systems.

Warfarin: Quinolones, including moxifloxacin, have been reported to enhance the anticoagulant effects of warfarin or its derivatives. In addition, infectious disease and its accompanying inflammatory process, age, and general status of the patient are risk factors for increased anticoagulant activity. If a quinolone is administered concomitantly with warfarin or its derivatives, the prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should closely monitored.

Sotalol, a class III antiarrhythmic has been shown to further increase the QTc interval when combined with high doses of intravenous moxifloxacin in dogs. Therefore moxifloxacin should be avoided with class IA and class III antiarrhythmics.

Although not observed with moxifloxacin in preclinical and clinical trials, the concomitant administration of a nonsteroidal anti-inflammatory drug with a quinolone may increase the risks of CNS stimulation and convulsions.

1.1.n Dosing and Administration

The recommended dose of oral or intravenous moxifloxacin is 400 mg once every 24 hours. The duration of therapy depends on the type of infection. Moxifloxacin tablets can be taken with or without food. When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. For infections due to the designated pathogens:

Indications:	Daily Dose	Duration
Acute bacterial exacerbation of chronic bronchitis (ABECB)	400 mg	5 days
Acute bacterial sinusitis (ABS)	400 mg	10 days
Community-acquired pneumonia (CAP)	400 mg	7-14 days
Uncomplicated skin and skin structure infections (uSSSI)	400 mg	7 days
Complicated skin and skin structure infections (cSSSI)	400 mg	7-21 days

τ Videx® is a registered trademark of Bristol-Myers Squibb Company.

Oral doses of moxifloxacin should be administered at least 4 hours before or 8 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or didanosine (VIDEX®) chewable/buffered tablets or the pediatric powder for oral solution.

Intravenous moxifloxacin should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-site type intravenous infusion. Rapid or bolus intravenous infusion must be avoided. Additionally, since limited data are available about the compatibility of moxifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to the moxifloxacin intravenous preparation or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of other drugs, the line should be flushed before and after infusion of moxifloxacin with a compatible diluent.

1.1.o Access

No information is currently available with regard to potential restrictions on distribution and supply, or anticipated shortages.

1.1.p Co-Prescribed/Concomitant Therapies

N/A

1.1.r Comparison with Pharmacokinetic/Pharmacologic Profile of Other Agents in Therapeutic Area

Comparison of Moxifloxacin to Other Broad Spectrum Quinolone Antibacterial Agents based on product specific Product Information Sheets.

Drug	Bioavailability	Volume of Distribution (L/kg)	Metabolism/ Excretion	Elimination Half-Life (oral dose) (Hours)	Dosage adjustment recommendations for renal or hepatic impaired patients
Moxifloxacin (Avelox®)	~ 90%	1.7 to 2.7	Liver; glucuronide, and sulfate conjugation, 45% excreted as unchanged drug in the urine	12 hours	**Renal** - No **Hepatic** - No
Ciprofloxacin (Cipro®)	~ 70%	1.2 to 2 (Brittain et al., 1985)	Liver; 4 metabolites have been identified and account for 15% of an oral dose, eliminated primarily by renal excretion	4 hours	**Renal** - Yes – in patients with creatinine clearance =50 ml/min **Hepatic** - No
Gatifloxacin (Tequin®)	~ 96%	1.5 to 2	Liver; minimal primarily excreted unchanged in the urine	7 to 14 hours	**Renal –** Yes – in patients with creatinine clearance <40 ml/min **Hepatic** - No – in mild hepatically impaired patients
Gemifloxacin (Factive®)	~ 71%	1.66 to 12.12	Liver, minimal primarily excreted unchanged in feces and urine	4 to 12 hours	**Renal** - Yes – in patients with creatinine clearance =40 ml/min **Hepatic** - No – in mild, moderate or severe hepatic impairment
Ofloxacin (Floxin®)	~ 98%		Liver, minimal primarily (65 to 80%) excreted in the urine	9 hours	**Renal** - Yes – in patients with creatinine clearance =50 ml/min **Hepatic** – Yes – patients with severe liver function disorders should receive a maximum of 400 mg per day.
Levofloxacin (Levaquin®)	~ 99%	1.1-1.6	Liver; minimal primarily excreted unchanged (87%) in the urine	6 to 8 hours	**Renal** - Yes - in patients with renal impairment (see product labeling for specific recommendations) **Hepatic** - No

PI = prescribing information.

These comparisons are meant for informational purposes.

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Tequin® is a registered trademark of Bristol-Myers Squibb Company.
Levaquin® is a registered trademark of Ortho-McNeil Pharmaceutical, Inc.
Factive® is a registered trademark of Oscient Pharmaceuticals.
Floxin® is a registered trademark of Ortho-McNeil Pharmaceutical, Inc.

In Vitro* Activity

Organism	MIC_{90} (mg/ml)					# of strains	Ref.
	Moxifloxacin	Gemifloxacin	Gatifloxacin	Levofloxacin	Ciprofloxacin		
S. pneumoniae	0.25	0.06	0.5	2	4	769	Blondeau 2003
H. influenzae	0.03	0.016	0.016	0.016	0.016	699	Blondeau 2003
M. catarrhalis	0.06	0.008	0.03	0.06	0.03	313	Blondeau 2003
C. pneumoniae	0.06	NA[Y]	NA[Y]	0.5	2	15	Miyashita 2002
M. pneumoniae	0.12	0.12	0.12	1	4	97	Waites 2003
L. pneumophila	0.008-0.016	0.016-0.03	NA[Y]	0.008-0.016	0.016-0.06	198	Dubois 2000

***** The clinical relevance of *in vitro* data is unknown. *In vitro* data does not necessarily imply clinical effectiveness. Please see full prescribing information for respective products.
[Y] Not available.

References for Section 1.1

Avelox® Prescribing Information.

Brittain DC, Scully BE, McElrath MJ, et al. The pharmacokinetics and serum and urine bactericidal activity of ciprofloxacin. *J Clin Pharmacol*. 1985;25:82-88.

Cipro® Prescribing Information, 10/2004.

Levaquin® Prescribing Information, 8/2005.

Tequin® Prescribing Information, 5/2005.

Floxin® Prescribing Information, 8/2004.

Factive® Prescribing Information, 8/2004.

Blondeau *et al*. *Int J Antimicrob Agents*. 2003 Aug;22(2):147-54.

Miyashita *et al*. *J Infect Chemother*. 2002 Mar;8(1):115-7.

Waites *et al*. *Int J Antimicrob Agents*. 2003 Jun;21(6):574-7.

Dubois and St-Pierre *Antimicrob Chemother*. 2000 Apr;45 Suppl 1:41-6.

1.2 Place of the Product in Therapy

1.2.1 Community Acquired Pneumonia (CAP)

Summary

Community-acquired pneumonia (CAP) remains a common and serious illness, in spite of the availability of potent new antimicrobials (Niederman et al, 2001). The empiric antimicrobial treatment regimens for CAP are based upon an assessment of the likelihood that a given pathogen is causing the disease, the severity of the illness, and the known sensitivities of pathogens in the community. All regimens should cover *Streptococcus pneumoniae* as the most likely pathogen (Bartlett et al, 2000). The decision to change the route of administration from intravenous to oral antibiotic therapy is based on an assessment by a health care provider of clinical response, with the evaluation of symptoms of cough, sputum production, dyspnea, fever, and leukocytosis. Once the patient has clinically stabilized, transitioning to oral therapy can be achieved. Among the new fluoroquinolones, moxifloxacin has a low MIC_{90} for *Streptococcus pneumoniae* and has coverage for other Gram-positive bacteria that cause CAP (*Haemophilus influenzae, Moraxella catarrhalis, Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*). Moxifloxacin is rapidly acting and bactericidal *in vitro*[*] (Avelox PI).

1.2.1.a Epidemiology and Relevant Risk Factors

CAP remains a common and serious illness. In the United States, CAP is the sixth leading cause of death and the most common infectious cause (Bartlett et al, 2000, Niederman et al, 2001). More than 80% of cases of CAP are managed in the community, where the mortality rate is around 1%. Among those approximately 500,000 patients admitted to the hospital each year, 10%-14% will die, with the mortality rate rising to 30%-40% for those requiring intensive care (Bartlett et al, 2000). Approximately 10% of CAP cases are severe enough to require intensive care and/or mechanical ventilation. The aging population, increased prevalence of comorbid illnesses, infection with human immunodeficiency virus, and increasing microbial resistance probably all have contributed to maintaining the high mortality rate despite advances in medical care. Pneumonia is increasingly being recognized among older patients and those with comorbidity (coexisting illness) such as chronic obstructive lung disease, diabetes mellitus, renal insufficiency, congestive heart failure, coronary artery disease, malignancy, chronic neurologic disease, and chronic liver disease (Ruiz et al, 1999).

Morbidity and cost due to CAP are difficult to measure. Annual CAP patient treatment costs were $9.7 billion in 1994; 92% of these costs were associated with inpatient therapy. There is substantial disparity in cost between an episode of inpatient and outpatient therapy ($7,517 versus $264) (Lave et al, 1999).

There are numerous risk factors for CAP, including advancing age and comorbidities. Risk factors have been identified, studied, and incorporated into a clinical prediction rule. The information below details and incorporates the risk factors for CAP and identifies patients at higher risk for substantial morbidity from CAP.

[*] The clinical relevance of *in vitro* data is not known.

Pneumonia Severity Index (PSI) Clinical Prediction Rule – The PSI rule was derived and validated as part of the Pneumonia Patient Outcomes Research Team (PORT) prospective cohort study for the purpose of identifying patients with CAP at low risk for mortality versus those requiring more intensive care (Fine et al, 1997, 1993, 1990). Patients with CAP are scored on the basis of risk classification as outlined in Tables 1.2.1.1 and 1.2.1.2 (Fine et al, 1997).

Table 1.2.1.1. Scoring System for CAP

Patient Characteristic	Points Assigned	Patient Characteristic	Points Assigned
Demographic Features		**Physical Examination Findings**	
Age		Altered mental status	+20
Males	Age in years	Respiratory rate ≥ 30/minute	+20
Females	Age in years – 10	Systolic BP < 90 mm Hg	+20
Nursing home resident	Age in years +10	Temperature < 35°C or ≥ 40°C	+15
		Pulse ≥ 125/minute	+10
Comorbid Illnesses		**Laboratory or Radiographic Findings**	
Neoplastic disease	+30	pH < 7.35	+30
Liver disease	+20	BUN ≥ 30 mg/dL	+20
Congestive heart failure	+10	Sodium < 130 mEq/L	+20
Cerebrovascular disease	+10	Glucose > 250 mg/dL	+10
Renal disease	+10	Hematocrit < 30%	+10
		PO_2 < 60 mm Hg or SaO_2 < 90%	+10
		Pleural effusion	+10

Table 1.2.1.2. Risk Class – Based on Cumulative Number of Points from Table 1.2.1.1.

Risk Class	No. of Points	Mortality (%)	Recommendations for Site of Care
I	Age < 50 years, no comorbidity, no PE findings	0.1	Outpatient
II *low*	≤ 70	0.6	Outpatient
III	71-90	2.8	Inpatient (briefly) or outpatient
IV *moderate*	91-130	8.2	Inpatient
V *high*	> 130	29.2	Inpatient (likely ICU)

PE = physical examination.

1.2.1.b Pathophysiology

Most types of pneumonia are related to acquired infection in the nasopharynx (bacteria in the nose and throat) that is carried into the lower respiratory tract (lungs). The incidence of disease increases strongly in association with or following a viral illness, e.g., influenza. Other risk factors for CAP include advancing age, underlying lung disease, other chronic diseases, and a suppressed immune system.

The most common bacterial cause of CAP is *Streptococcus pneumoniae* (16%-76%), followed by *Mycoplasma pneumoniae* (25%), *Chlamydia pneumoniae* (< 18%), and *Haemophilus influenzae* (10%) (File, 2003). Other less common bacterial causes of CAP are *Legionella* spp., *Staphylococcus aureus*, Gram-negative bacilli, and anaerobic bacteria. *Streptococcus pneumoniae* is acquired in the nasopharynx and carried asymptomatically in approximately 50% of individuals at any point in time (Austrian, 1986). Invasive disease most commonly occurs upon acquisition of a new serotype of bacteria, typically after an incubation period of 1-3 days.

1.2.1.c Clinical Presentation

The diagnostic approach for CAP rests upon three main parameters:

- Clinical presentation – Patients with CAP classically present with the sudden onset of rigors (chills) followed by fever, pleuritic chest pain (chest pain with deep breathing or "pleurisy"), and cough productive of purulent sputum.
- Chest x-ray – The presence of an infiltrate on chest x-ray is considered the "gold standard" for diagnosing pneumonia when clinical and microbiologic features are also supportive. A chest x-ray is obtained in most patients.
- Sputum evaluation – Blood cultures and basic blood work are often obtained in patients that are hospitalized for CAP (see Tables 1 and 2 above for hospitalization criteria).

The patient characteristics, risk factors, and sometimes the appearance of abnormalities on the chest x-ray are used as clues to suggest whether the etiology of CAP is characteristic of an atypical pathogen. However, while these parameters are good indicators of the presence of pneumonia, they have been shown not to be very sensitive predictors of the etiologic agent of pneumonia. Therefore, the recommendations and guidelines indicate empiric therapy for most persons presenting with CAP, as discussed below.

1.2.1.d Approaches to Treatment – Principal Options/Practice Patterns

There is much debate in the literature about whether initial therapy for pneumonia should be empiric or based upon clinical features (clinical presentation, immune status, and chest radiograph findings) and Gram stain of respiratory secretions (evaluation of the sputum with staining and microscopic evaluation).

Empiric regimens – The American Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA), and the Antibiotic Selection for Community-Acquired Pneumonia (ASCAP) Consensus Panel Report have put forth guidelines for empiric therapy of CAP determined by the patient's underlying medical condition and the severity of illness as defined by the need for hospitalization (Niederman et al, 2001, Mandell et al, 2003, ASCAP Consensus Report, 2005). The antibiotic regimens advocated by these groups are summarized in the tables below. The ATS and IDSA Guidelines for CAP are shown in Table 1.2.1.3, and the ASCAP Consensus Panel Report Guidelines for CAP are shown in Table 1.2.1.4.

Recommendation summary:

- For uncomplicated pneumonia in patients who do not require hospitalization, an advanced macrolide such as azithromycin or clarithromycin is recommended.
- For a hospitalized patient, ceftriaxone with or without azithromycin (depending upon the likelihood of an atypical organism) is recommended. For more severely ill patients who might have an atypical pneumonia or patients admitted to an intensive care unit, therapy is initiated with a fluoroquinolone or azithromycin to treat *Legionella* spp. infection as well as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.
- The IDSA guidelines favor use of newer respiratory fluoroquinolones (e.g., moxifloxacin, levofloxacin, gatifloxacin), which have better coverage versus *Streptococcus pneumoniae* than ciprofloxacin (Mandell et al, 2003).
- The ASCAP Guidelines indicate that moxifloxacin is the preferred fluoroquinolone for the treatment of outpatients with CAP (ASCAP Consensus Report, 2005).

Table 1.2.1.3. Treatment Guidelines for CAP from the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA)

Patient Setting	ATS Guidelines 2001	IDSA Guidelines 2003
Outpatient	***Without cardiopulmonary disease or other modifying factors:*** Advanced generation macrolide: azithromycin or clarithromycin *- or -* Doxycycline ***With cardiopulmonary disease or other modifying factors:*** β-Lactam (oral cefpodoxime, cefuroxime, high-dose amoxicillin, amoxicillin/clavulanate; or parenteral ceftriaxone followed by oral cefpodoxime) *plus* macrolide or doxycycline *- or -* Antipneumococcal fluoroquinolone (used alone)	***No recent antibiotic therapy:*** Macrolides or doxycycline Penicillin-resistant *S. pneumoniae* may be resistant to macrolides and/or doxycycline ***Recent antibiotic therapy (3 mo):*** Respiratory fluoroquinolone alone - or - Advanced macrolide + high-dose amoxicillin or high-dose amoxicillin-clavulanate
Hospitalized patients (on general ward or not in ICU)	***Without cardiopulmonary disease or other modifying factors:*** Intravenous azithromycin alone If macrolide allergic or intolerant: Doxycycline and a ß-lactam *- or-* Monotherapy with an antipneumococcal fluoroquinolone ***With cardiopulmonary disease or other modifying factors:*** Intravenous ß -lactam (cefotaxime, ceftriaxone, ampicillin/sulbactam, high-dose ampicillin) *plus* intravenous or oral macrolide or doxycycline *-or -* Intravenous antipneumococcal fluoroquinolone alone	Respiratory fluoroquinolone alone *- or -* Advanced macrolide + β-lactam
Hospitalized patient in ICU	***For patients without a risk factor for Pseudomonas aeruginosa*:** IV β-lactam + either IV macrolide (e.g., azithromycin) *- or -* IV fluoroquinolone ***For patients with a risk factor for Pseudomonas aeruginosa*:** Selected intravenous antipseudomonal β-lactam (cefepime, imipenem, meropenem, piperacillin/ tazobactam) *plus* intravenous antipseudomonal quinolone (ciprofloxacin) *- or -* Selected intravenous antipseudomonal β-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) *plus* intravenous aminoglycoside *plus either* intravenous macrolide (azithromycin) *- or -* Intravenous nonpseudomonal fluoroquinolone	***No b-lactam allergy, no concerns about Pseudomonas aeruginosa*:** β-Lactam + respiratory fluoroquinolone or advanced macrolide ***b-Lactam allergy:*** Respiratory fluoroquinolone, ± clindamycin

Table 1.2.1.4: Treatment Guidelines for CAP from the Antibiotic Selection for Community-Acquired Pneumonia (ASCAP) Consensus Panel, 2005

Patient Profile	First-Line Antibiotic Therapy	Alternative First-Line Antibiotic Therapy
Otherwise healthy outpatients	Azithromycin p.o.	Telithromycin p.o. (preferred) *or* Moxifloxacin p.o. *or* Levofloxacin p.o. *or* Clarithromycin *or* Gatifloxacin p.o. *or* Doxycycline p.o.
Comorbidity present in outpatients	Moxifloxacin p.o. (preferred) *or* Telithromycin p.o.	Levofloxacin p.o. *or* Azithromycin p.o. *or* Clarithromycin *or* Gatifloxacin p.o.
Hospitalized (non-ICU)	Ceftriaxone IV + azithromycin IV	Moxifloxacin IV (preferred) *or* Levofloxacin IV *or* Gatifloxacin IV
Nursing home-acquired CAP and managed in hospital	Ceftriaxone IV + azithromycin IV	Levofloxacin IV (preferred) *or* Moxifloxacin IV *or* Gatifloxacin IV
CAP acquired and managed in the nursing home	Ceftriaxone IV or IM + azithromycin IV or p.o. *or* Levofloxacin IV or p.o.	Moxifloxacin IV or p.o. *or* Gatifloxacin IV or p.o. *or* Amoxicillin-clavulanate p.o. + azithromycin p.o.
Severe bacteremic CAP with likely *S. pneumoniae* species with risk factors for resistance to macrolides	Ceftriaxone IV + moxifloxacin IV	Ceftriaxone IV + levofloxacin IV
Suspected MRSA CAP (i.e. severe CAP in compromised host)	Moxifloxacin IV + linezolid IV *or* Moxifloxacin IV + vancomycin IV	Levofloxacin IV + vancomycin IV *or* Ceftriaxone IV + azithromycin IV + linezolid IV
Severe CAP requiring ICU hospitalization (*Pseudomonas* not suspected)	Ceftriaxone IV + levofloxacin IV *or* Ceftriaxone IV + moxifloxacin IV	Ceftriaxone IV + azithromycin IV

1.2.1.e Description of Alternative Treatment Options

N/A

1.2.1.f Place of Moxifloxacin in Treatment

The need for targeted and appropriate first-line treatment in patients with recurrent respiratory infections has rapidly become apparent. Emerging resistance to antimicrobial agents by pathogens, such as *Streptococcus pneumoniae*, further underlines the importance of appropriate antimicrobial treatment. Since 1999, case reports of failure of therapy with levofloxacin have started to appear, and in some cases, levofloxacin resistance has developed within days of the initiation of fluoroquinolone therapy (Low, 2004). The ASCAP guidelines list moxifloxacin as the

fluoroquinolone of choice, when a fluoroquinolone is indicated, for treating patients with CAP due to organisms sensitive to moxifloxacin, including *S. pneumoniae*. This recommendation is based on the facts that moxifloxacin has one of the lowest MIC values agains *S. pneumoniae* in it's class, it provides focused gram-positive coverage, and attains higher concentrations in the lung fluid compared to levofloxacin (ASCAP Consensus Report, 2005). The IDSA includes moxifloxacin as an initial therapy in guidelines for the treatment of uncomplicated CAP (Mandell, 2003). Recommendations for the treatment of patients who are hospitalized (moderately or critically ill) currently consist of empiric therapy with either monotherapy with a fluoroquinolone such as moxifloxacin or an extended-spectrum macrolide. The impact of implementing guidelines for the treatment of CAP was assessed within a rural referral hospital, and the percentage of patients receiving appropriate antibiotic therapy increased from 67% to 87% (Santos et al, 2004). The mean length of hospital stay decreased by 1 day, and the average charge per patient decreased by $829 in the post-intervention group ($205,000 per year savings) (Santos et al, 2004).

Moxifloxacin is convenient to use in both the community and the hospital setting and has a proven safety and tolerability record. Moxifloxacin has targeted activity against *Streptococcus pneumoniae* (including multi-drug resistant strains), *Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae*. *In vitro*[*] studies have demonstrated moxifloxacin achieves drug concentrations at least three times higher in lung tissues than the older fluoroquinolones levofloxacin or ciprofloxacin (Mandell et al, 2004). Moxifloxacin has shown higher steady state drug levels in the alveolar macrophages and epithelial lining fluid as well as maintaining mean concentrations above the MIC_{90} value for *S. pneumoniae* when compared to levofloxacin in healthy human subjects (Capitano et al, 2004).

Clinical studies have demonstrated that moxifloxacin monotherapy is as effective (Katz et al, 2004; Lode, 2004; Torres, 2003; File et al, 2001; Hoeffken, 2001; Fogarty, 1999) or more effective (Finch et al, 2002) than comparator combination regimens, including β-lactams, macrolides, and/or fluoroquinolones. Moxifloxacin (IV, 400 mg QD) followed by p.o. (400 mg QD) for 7-14 days had superior clinical success rates (93% vs 85%) and superior bacterial eradication (94% vs 82%), and moxifloxacin-treated patients were afebrile in a shorter time (by day 2, 59% vs 47%) than comparator-treated patients (IV co-amoxiclav,[γ] 1.2 g t.i.d., followed by p.o. co-amoxiclav, 625 mg, t.i.d., with or without IV/p.o. clarithromycin, 500 mg b.i.d. for 7-14 days) in 628 adult patients with CAP requiring initial parenteral therapy (Finch et al, 2002).

[*] The clinical relevance of *in vitro* data is not known.

[γ] Not available in the US.

Table 1.2.1.5. Finch et al, 2002

Sample characteristics – No. of patients				Treatment and dosage regimens
	Moxifloxacin	**Comparator**	**Total**	
Enrolled	306	322	628	**Moxifloxacin** – 400 mg IV qd followed by 400 mg po qd x 7-14 d
ITT	301 (98%)	321 (100%)	622	
PP	258 (84%)	280 (87%)	538	
Non-severe pneumonia	129 (50%)	143 (51.1%)	272	**Comparator** – Co-amoxiclav 1200 mg IV tid followed by co-amoxiclav 625 mg po tid with or without clarithromycin 500 mg bid (iv or po) x 7-14 d
Severe pneumonia	129 (50%)	137 (48.9%)	266	
ITT=intent to treat; PP=per protocol				

Efficacy analysis (PP Population)			
	Moxifloxacin (n=258)	**Comparator (n=280)**	**% ? (95% CI)**
Clinical cure at TOC	241 (93.4%)	239 (85.4%)	8.0[a] (2.9-13.2)
Clinical cure at follow up	216 (83.7%)	208 (74.3%)	9.4 (2.6-16.3)
Bacteriological success[b] at TOC (5-7 days post-treatment))	60 (93.7%)	58 (81.7%)	12.1 (1.2-22.9)
Bacteriological success[b] at follow up (21-28 days post-treatment)	54 (84.4%)	50 (70.4%)	14.0 (0.0-28.0)

a By test of superiority, $P = 0.004$.

b Eradication and presumed eradication in microbiologically valid patients.

A faster change in route of administration, from IV to oral, by day 5 was observed for patients receiving moxifloxacin than comparator in severe CAP (73% vs 60% for moxifloxacin and the comparator, respectively, p<0.01) (Lode et al, 2003). Thus, clinical studies demonstrate the success of moxifloxacin monotherapy in hospitalized CAP. In summary, the overall results for the trials discussed above are summarized in Table 1.2.1.6.

Table 1.2.1.6. Results of Select Comparative Trials for the Treatment of CAP

Study	Trial Design	Comparator	Results
Lode 2003	Data pooled from 2 prospective, randomized, multi-national studies	IV/p.o. moxifloxacin vs amoxi/clav ± clarithromycin or IV/p.o. moxifloxacin vs trovafloxacin or levofloxacin	▪ Similar clinical and bacteriologic success rates between the groups ▪ Moxifloxacin had a faster IV to PO transition in severe CAP (p<0.01)
Finch 2002	Multi-national, multi-center, randomized, controlled, open-label trial	IV/p.o. moxifloxacin vs amoxi/clav ± clarithromycin	▪ Moxifloxacin had superior clinical outcome (p=0.004) ▪ Moxifloxacin had superior bacterial eradication ▪ Moxifloxacin patients were afebrile in a shorter time
Katz 2004	Multi-center, prospective, randomized, open-label trial	IV/p.o. moxifloxacin vs IV ceftriaxone/p.o. cefuroxime ± azithromycin ± metronidazole	▪ Moxifloxacin monotherapy had outcomes similar to combination therapy

Few studies have prospectively evaluated CAP treatment in elderly patients. The CAPRIE study was designed as a prospective, third-party blind, double-dummy, multi-center trial to compare

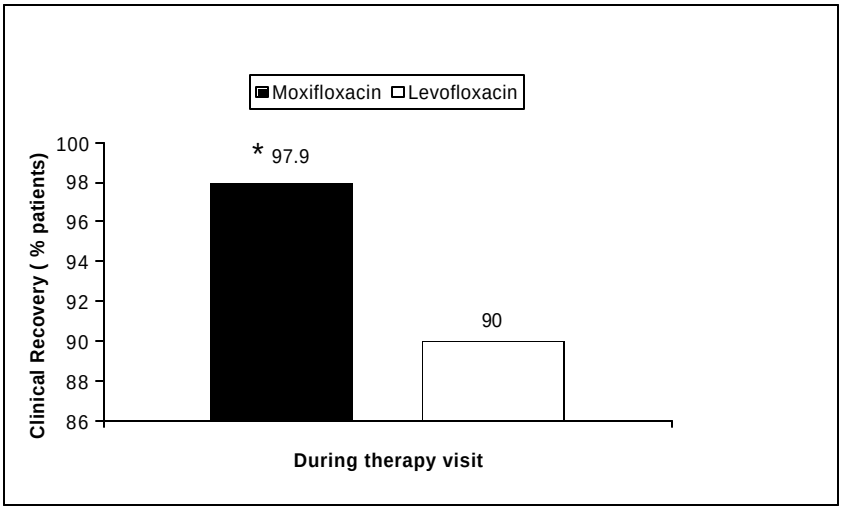
moxifloxacin and levofloxacin in elderly patients with community-acquired pneumonia (CAP) (Data on File, Study 10872/MRR-00140). Specifically, the CAPRIE trial compared the efficacy and safety of sequential intravenous (IV)/oral (PO) regimens of moxifloxacin and levofloxacin for the treatment of hospitalized elderly (at least 65 years of age) patients with CAP requiring initial parenteral therapy. Subjects enrolled in the trial were first stratified by disease severity using the revised American Thoracic Society severity criteria and risk class (Niederman et al, 2001) using the Pneumonia Outcome Research Team Severity Index score (Fine et al, 1997). Following this stratification, patients were randomized to receive moxifloxacin IV 400 mg daily or levofloxacin IV 500 mg daily. Patients could be transitioned to an oral regimen of moxifloxacin 400 mg daily or levofloxacin 500 mg daily after at least 2 days of therapy if they demonstrated improvement, were afebrile for at least 8 hours, were able to tolerate oral food/fluids/medications and were not experiencing vomiting or diarrhea. Patients were treated for a total of 7–14 days. The intent to treat population was 51% male, with a mean age of 77.8 years (63% were over 75 years). Most patients had multiple co-morbidities (74% cardiac, 63% COPD, 29% diabetes) with 18% having severe CAP as per the 2001 ATS guidelines, and 69% had a PSI of at least 3.

The primary endpoint of this study was to evaluate cardiac safety based on Holter monitor findings. Secondary endpoints included clinical response during treatment (3-5 days after initiating therapy) and clinical and bacteriologic response at the test-of-cure visit (5-21 days post-treatment). Patients were considered valid for the clinical efficacy analysis if they met the eligibility criteria for the trial, were treated for at least 48 hours (if a treatment failure) or 5 days (if a clinical cure), did not require concomitant systemic antimicrobial therapy and had a test-of-cure clinical assessment that was not indeterminate. These patients also had to be adherent to therapy by taking at least 80% of the medication administered to them. Clinical response during therapy was categorized as "Resolution" if acute signs and symptoms of infection disappeared, "Improvement" if there was a reduction in the severity or number of signs and symptoms, "Failure" if there was a failure to respond or insufficient decrease in the signs and symptoms of infection requiring additional or alternative antimicrobial therapy, or "Indeterminate" if it was not possible to determine response for any reason. Clinical response at the test-of-cure visit was categorized as "Cure" if the acute signs and symptoms of infection disappeared or there was sufficient improvement eliminating the need for any additional or alternative antimicrobial therapy, "Failure" if there was an insufficient decrease in the signs and symptoms of infection requiring additional or alternative antimicrobial therapy, or "Indeterminate" if the evaluation of response was not possible.

Of the 394 patients who received at least one dose of study drug (intent-to-treat population), 281 patients were considered clinically-valid for the efficacy analysis. There were 141 moxifloxacin patients and 140 levofloxacin patients in the clinically-valid population. Overall, the moxifloxacin and levofloxacin groups were well balanced for baseline characteristics and clinical presentation.

The duration of antimicrobial treatment for both treatment groups was 10 days in the clinically-valid population. The mean duration of IV therapy in the moxifloxacin group was 3.7 days and in the levofloxacin group was 3.8 days. A significantly faster recovery during treatment (resolution or improvement 3-5 days after initiating therapy) was reported for the moxifloxacin group (97.9% [138/141]) compared to the levofloxacin group (90.0% [126/140]). Recovery rates 3-5 days after initiating therapy are depicted below in Figure 1.2.1.1.

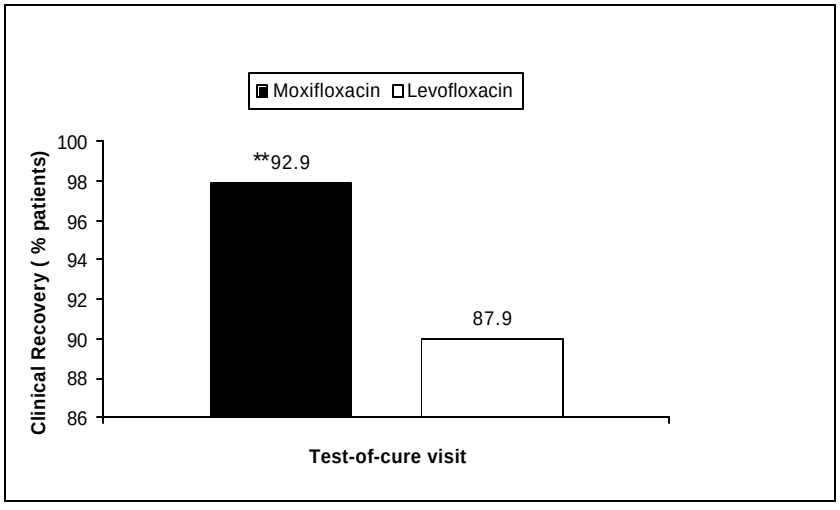
Figure 1.2.1.1: Recovery Rates at the during therapy visit (days 3-5)



*p=0.01

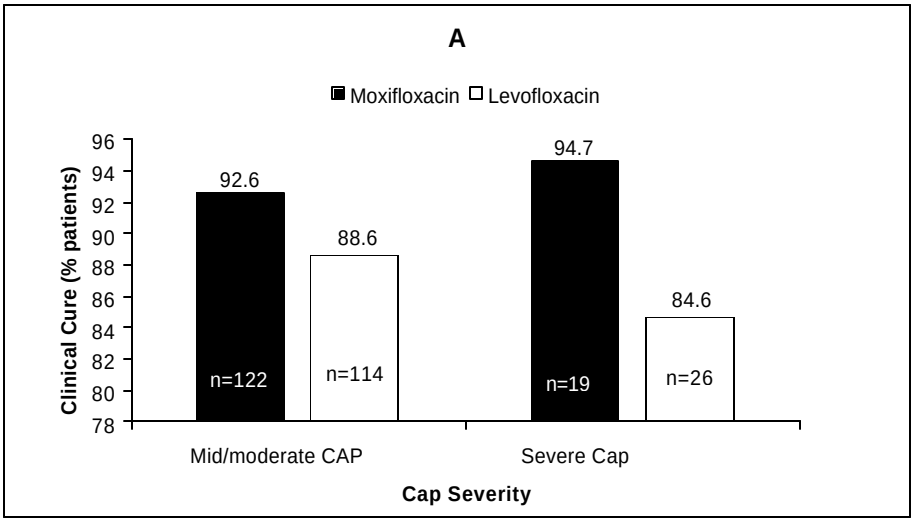
The overall clinical cure rate in this population at the test-of-cure visit, 5-21 days post-treatment, was 92.9% (131/141) for moxifloxacin and 87.9% (123/140) for levofloxacin (See Figure 1.2.1.2). The difference between these two groups was not statistically significant. The clinical cure rate for moxifloxacin was over 90% in the subgroups of patients with severe CAP and who were over 75 years old. Figure 1.2.1.3 below provides the clinical cure rates at the test of cure visit as stratified by CAP severity and age.

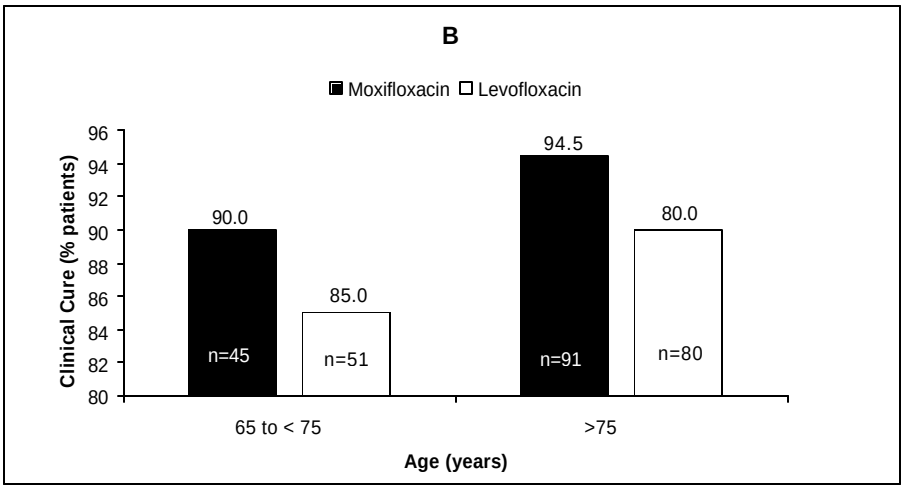
Figure 1.2.1.2. Clinical Cure Rate at the Test-of-Cure Visit, 5-21 Days Post-Treatment



**p=0.2

Figure 1.2.1.3: Clinical cure rates at the test-of-cure visit (5-21 days post-therapy) (clinically-valid population) stratified by (A) CAP severity; (B) age.





In the CAPRIE study, there was no significant difference between moxifloxacin and levofloxacin with respect to cardiac safety, the primary endpoint of the study. Additionally, the overall investigator-reported drug related adverse events were similar between moxifloxacin and levofloxacin. Treatment-emergent adverse events were reported in 164 moxifloxacin and 146 levofloxacin patients. Of these events, 46 moxifloxacin and 45 levofloxacin events were considered serious. The most common serious adverse events in both treatment groups included exacerbation of chronic obstructive pulmonary airway disease, nosocomial pneumonia, congestive heart failure, renal insufficiency, respiratory failure and atrial fibrillation. Fifteen moxifloxacin and 20 levofloxacin patients discontinued therapy due to an adverse event, of which 10 moxifloxacin and 7 levofloxacin cases were considered to be related to study drug. Mortality rate was 7.7% (15/195) for the moxifloxacin group and 5.5% (11/199) for the levofloxacin group. The majority of these deaths occurred over 7 days after the last dose of study drug was administered. Six moxifloxacin patients and 3 levofloxacin patients died during therapy or within 7 days post-therapy. None of the deaths were considered by investigators to be study drug-related but rather due to comorbid disease.

Of the adverse events reported during this trial, 51 moxifloxacin and 45 levofloxacin events were considered related to the study drug. The most common drug-related adverse events included diarrhea (5.6% moxifloxacin vs. 5.0% levofloxacin), oral candidiasis (3.6% moxifloxacin vs. 3.5% levofloxacin), nausea (1.5% moxifloxacin vs. 2% levofloxacin) and *Clostridium difficile* colitis (0.5% moxifloxacin vs. 3% levofloxacin). Cardiac events which were considered potentially drug-related occurred in 1% (2/195) of moxifloxacin patients and 3.5% (7/199) of levofloxacin patients. Ventricular tachycardia and supraventricular tachycardia were the 2 cardiac events in the moxifloxacin group. In the levofloxacin group, atrial fibrillation was the most common cardiac event. Additionally, one patient in the levofloxacin group reported one episode of torsade des pointes which resolved spontaneously.

1.2.1.g Expected Outcomes of Therapy – Resolution and Slow or Incomplete Resolution

The specific factors that are associated with improved patient outcomes include time to antibiotic administration, blood culture collection, and appropriate empirical antibiotic selection. The normal resolution of pneumonia is not easily defined and may vary depending upon the underlying cause, as well as the host. Patients typically note subjective improvement within 3 to 5 days of treatment. More specific clinical criteria for resolution include improvement in fever, cough, crackles, leukocytosis (elevated white blood cell count), and arterial oxygenation. However, most studies on the natural history of pneumonia have focused upon the resolution of chest radiographic abnormalities, with "slow resolution" often being defined as the persistence of radiographic abnormalities for > 1 month in a clinically improved host (Arancibia et al, 2000).

Slow or incomplete resolution of pneumonia despite treatment is a common clinical problem (Arancibia et al, 2000). There are a variety of reasons that pneumonia resolves slowly or incompletely, including those relating to the etiology of the pneumonia (misdiagnosis of the pathogen or the presence of a resistant pathogen), those relating to the host, and the development of complications from the initial infection. In addition, non-infectious etiologies of pulmonary infiltrates can mimic infectious pneumonia, thus making it appear that resolution is not following the expected course. Approximately 20% of presumed non-responding CAP is due to non-infectious causes (Arancibia et al., 2000).

The presence of a resistant pathogen is an important consideration for any pneumonia that is not responding appropriately to antibiotic therapy. Although penicillin-resistant *Streptococcus pneumoniae* is the organism of most concern, multi-drug-resistant *Haemophilus influenzae* and *Pseudomonas aeruginosa* as well as methicillin-resistant *Staphylococcus aureus* are possible causes of a non-resolving pneumonia.

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1.2.2 Acute Bacterial Sinusitis (ABS)

Summary

The primary goal of antibiotic therapy for ABS is to eradicate the bacterial pathogens from the site of infection, which helps to decrease the duration of symptoms and to allow patients to resume daily activities more quickly. Therapy should also return the sinuses back to health, prevent severe complications (e.g., meningitis and brain abscess), and decrease the likelihood of developing chronic disease. Primary care physicians frequently approach sinusitis as the manifestation of acute bacterial infection and prescribe an antibiotic in 85%-98% of cases. More than half of sinusitis sufferers require a second antibiotic. *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* are the bacteria most commonly isolated from infected maxillary sinuses. Increasing resistance to macrolide antibiotics has necessitated reevaluation of treatment recommendations for ABS. The newer fluoroquinolones have targeted *in vitro*[*] activity and have the advantage of once daily dosing (Anon et al, 2004). Moxifloxacin is rapidly acting and bactericidal *in vitro*[*] (Avelox PI).

1.2.2.a Epidemiology

Nearly 20 million cases of acute bacterial rhinosinusitis (ABS) are managed annually, at an estimated cost of $3.5 billion per year in the United States (Anon, 2004). Additionally, many persons experience symptoms of sinusitis but do not seek medical attention, indicating the true burden of sinusitis might be even higher than these estimates. Sinusitis is the fifth most common diagnosis for which antibiotics are prescribed. Sinusitis accounted for 21% of all adult antibiotic prescriptions written in 2002 (Anon, 2004).

The incidence of sinusitis is higher in the Midwest and South, compared with northeastern and western regions of the United States (Kaliner et al, 1997). Sinusitis is seasonal, with the highest rates in fall, winter, and spring, a time that overlaps with the peaking in incidence of perennial allergic rhinitis and viral upper respiratory infections (Laurier et al, 1999).

1.2.2.b Pathophysiology and Microbiology

The maxillary, frontal, ethmoid, and sphenoid sinuses all drain into the nasal cavity through ostia that are 1-3 mm in diameter. If these narrow openings are obstructed, an environment is created that facilitates bacterial colonization. Indeed, if obstruction caused by allergy or viral infection persists for 7-10 days, a secondary bacterial infection is likely. Thus, bacterial sinusitis is caused by the overgrowth of bacteria in a closed cavity, resulting in inflammation of the mucosa of the paranasal sinuses. Viral and bacterial infection causes obstruction and subsequent inflammation and edema, and this inflammation reduces mucociliary function resulting in stagnation of secretions, decreased pH, and lowered oxygen tension. This provides an ideal environment for bacterial multiplication (Fagnan, 1998).

Because the paranasal mucosa and the nasal epithelium are contiguous, the disorder is also called rhinosinusitis. Bacterial sinusitis is usually preceded by viral or allergic rhinitis. Sinusitis without rhinitis is rare. Other factors that may predispose a person to sinusitis include concurrent group A streptococcal infection, allergic rhinitis, environmental pollutants, dental infections, swimming, asthma, and anatomic variations (Gooch et al, 2000).

[*] The clinical relevance of *in vitro* activity is not known.

The most common bacterial isolates recovered from the maxillary sinuses of patients with ABS are S*treptococcus pneumoniae* (20%-43%), *Haemophilus influenzae* (22%-35%), and *Moraxella catarrhalis* (2%-10%) (Sinus and Allergy Health Partnership, 2004). Other *Streptococcus* species, anaerobic bacteria, and *Staphylococcus aureus* are found in a small percentage of cases. Fungi may cause sinusitis in patients with diabetes or who are immunocompromised.

1.2.2.c Clinical Presentation

The clinical presentation of ABS is difficult to distinguish from viral rhinosinusitis. To complicate the distinction, viral rhinosinusitis frequently precedes bacterial sinusitis. In general, symptoms of bacterial sinusitis worsen after 5 days, persist for at least 10 days, and are more severe (Sinus and Allergy Health Partnership, 2004). Most family physicians rely on four factors to distinguish bacterial sinusitis from a viral process: sinus tenderness, facial pressure, post-nasal drainage, and discolored post-nasal drainage (Hueston et al, 1998). The American Academy of Otolaryngology's Sinus and Allergy Health Partnership has developed clinical criteria for diagnosis of ABS (Sinus and Allergy Health Partnership, 2004). Major clinical factors (at least 2 must be present for diagnosis) include facial pain or pressure (especially when unilateral), facial congestion or fullness, nasal obstruction, nasal purulence or discolored postnasal discharge, hyposmia or anosmia, and fever. Minor clinical factors include headache, halitosis, fatigue, dental pain, cough, and ear pain, pressure, or fullness.

1.2.2.d Approaches to Treatment

Antibiotics are used to treat ABS because they produce more rapid resolution of symptoms. Perhaps even more importantly, antibiotics may decrease the rate of complications such as development of chronic sinusitis, facial osteomyelitis, cavernous sinus thrombosis, meningitis, orbital cellulitis or abscess, or brain abscess. Antibiotic treatment also may prevent acute sinusitis from developing into chronic sinusitis by preventing permanent mucosal damage.

To determine a treatment choice on the basis of patient and diagnosis, treatment recommendations have been outlined by a leading ENT organization, the Sinus and Allergy Health Partnership for acute bacterial rhinosinusitis of the American Academy of Otolaryngology-Head and Neck Surgery (AAOHNS) for 2004 (Table 1.2.2.1) (Sinus and Allergy Health Partnership, 2004). According to these guidelines, fluoroquinolones have the greatest predictive efficacy in adults with moderate ABS, as compared with macrolides, amoxicillin, and cefuroxime. Moxifloxacin is one of several antibiotics recommended as initial therapy for adults with moderate disease or who have received antibiotics in the past 4-6 weeks as well as for mild to moderately ill patients with β-lactam allergies. According to the guidelines, moxifloxacin and other fluoroquinolones also have a more favorable pharmacodynamic profile against *Streptococcus pneumoniae* and *Haemophilus influenzae* than macrolides. According to the Antibiotic Therapy for Bacterial Sinusitis (ATBS) Clinical Consensus Panel Report 2004, moxifloxacin is an alternative first-line antibiotic therapy for ABS in otherwise healthy patients without comorbid conditions with > 7 days of persistent symptoms or < 7 days of severe symptoms suggestive of bacterial rhinosinusitis (Table 1.2.2.2) (Bosker et al, ATBS Clinical Consensus Panel Report, 2004). Most published reviews of treatment for ABS recommend that the initial line of therapy should be an inexpensive agent such as amoxicillin or trimethoprim/sulfamethoxazole. In some parts of the United States, there is increasing penicillin-resistance among *Streptococcus pneumoniae* isolates; resistance of both *Haemophilus influenzae* and *Streptococcus pneumoniae* to trimethoprim/sulfamethoxazole has also increased substantially in recent years (Thornsberry et al, 1999). Other risk factors prompting consideration of use of another agent include antibiotic use in the last month, failure of the initial agent, infection despite

prophylactic treatment, smoker in family, frontal or sphenoidal sinusitis, or presentation with protracted (> 30 days) symptoms (Gooch et al, 2000).

Other agents that are considered effective because of their spectrum of activity and ease of administration include 2nd and 3rd generation cephalosporins such as cefpodoxime proxetil, cefprozil, cefuroxime axetil, and cefdinir. Amoxicillin/clavulanate has also been used in ABS. The newer macrolides, azithromycin and clarithromycin, are acceptable agents for treatment of ABS although resistance among *Streptococcus pneumoniae* isolates to these agents is increasing (Thornsberry et al, 1999; Thornsberry et al, 1997).

Table 1.2.2.1. Sinus and Allergy Health Partnership of the American Academy of Otolaryngology-Head and Neck Surgery (AAOHNS) Guidelines, 2004

Severity	Prior Antibiotics (4-6 Weeks)	Initial Therapy	Switch Therapy Options
Mild	No	Amoxicillin/clavulanate Amoxicillin Cefpodoxime Cefuroxime Cefdinir	Moxifloxacin, gatifloxacin, levofloxacin Amoxicillin/clavulanate Ceftriaxone Combination therapy
	β-Lactam allergic	Trimethoprim/sulfamethoxazole Doxycycline Azithromycin, clarithromycin	Moxifloxacin, gatifloxacin, levofloxacin Rifampin + clindamycin
	Yes	Moxifloxacin, gatifloxacin, levofloxacin Amoxicillin/clavulanate Ceftriaxone	Reevaluate patient
Moderate	β-Lactam allergic	Moxifloxacin, gatifloxacin, levofloxacin Amoxicillin/clavulanate Ceftriaxone	Reevaluate patient
		Moxifloxacin, gatifloxacin, levofloxacin Rifampin + clindamycin	Reevaluate patient

Table 1.2.2.2. Acute Bacterial Rhinosinusitis: Adult Treatment Guidelines from the Antibiotic Therapy for Bacterial Sinusitis (ATBS) Clinical Consensus Panel Report 2004

Otherwise Healthy Patients Without Comorbid Conditions with > 7 Days of Persistent Symptoms or < 7 days of Severe Symptoms Suggestive of Bacterial Rhinosinusitis
First-Line Antibiotic Therapy:
Amoxicillin/clavulanate extended release 2000 mg/125 mg p.o. b.i.d. × 10 days (Alternative: amoxicillin/clavulanate 500 mg/125 mg p.o. t.i.d. x 10 days)
OR
Amoxicillin 875 mg p.o. b.i.d.× 10-14 days
OR
Azithromycin 500 mg p.o. QD × 3 days
First-Line Alternative Antibiotic Therapy:
Moxifloxacin 400 mg p.o. QD × 10 days (preferred fluoroquinolone)
OR
Levofloxacin 500 mg p.o. QD × 10-14 days
OR
Clarithromycin 500 mg p.o. b.i.d. × 14 days
OR
Doxycycline 100 mg p.o. b.i.d. × 10-14 days

1.2.2.e Alternative Treatments

Adjunctive, non-antibiotic therapies for patients with acute sinusitis are aimed at decreasing edema to improve drainage and at promoting ciliary function. To improve ciliary function and decrease facial pain and congestion, some physicians recommend sipping hot fluids, applying moist heat with a hot towel, and inhaling steam. Salt water nasal rinses may be used to remove crusts and secretions. Other non-antibiotic treatments frequently used to treat sinusitis include oral or topical decongestants and mucolytic agents to thin secretions.

1.2.2.f Place of Moxifloxacin in Treatment

Important changes have been occurring in the epidemiology and resistance patterns for antibiotics used as first-line therapy in patients with ABS. The increasing prevalence of penicillin non-susceptible isolates of *Streptococcus pneumoniae* is a problem in the United States. Fluoroquinolones are increasingly being used as empiric therapy for the management of community-acquired respiratory tract infections, in part because of prevalent resistance to more traditional agents. Among the advanced generation, respiratory fluoroquinolones, moxifloxacin is preferred because it has lower MICs *in vitro*[*] against *Streptococcus pneumoniae* than levofloxacin and because it has a more targeted (Gram-positive organism-focused) spectrum of coverage (Bosker et al, ATBS Clinical Consensus Panel Report, 2004). In the 2004 treatment guidelines from the Sinus and Allergy Health Partnership, moxifloxacin is recommended for mild ABS with prior antimicrobial use in the past 4-6 weeks or for moderate ABS (Sinus and Allergy Health Partnership, 2004).

In vitro studies[*] have shown moxifloxacin eradicated *Streptococcus pneumoniae* more rapidly (Lister et al, 2001) and had four times more activity against *Streptococcus pneumoniae* than older quinolones levofloxacin or ciprofloxacin (Ball, 2000). Moxifloxacin HCl has also been shown to

[*] The clinical relevance of *in vitro* data is not known.

rapidly penetrate (within 2-4 hours) into sinus tissue, with concentrations exceeding MIC_{90}s for common sinus pathogens for over 40 hours (Gehanno et al, 2002).

Clinical studies support the use of moxifloxacin in ABS. Two randomized, double-blind multi-center trials showed that resolution-of-illness rates were high (90%) with moxifloxacin, and were comparable to those observed with commonly used drugs such as other fluoroquinolones and cefuroxime (Baz et al, 1999; Burke et al, 1999). Moxifloxacin proved to be more effective clinically and bacteriologically when compared to cefuroxime axetil in a prospective, multi-center, randomized study (Siegert et al, 2000). In this study, moxifloxacin demonstrated a statistically higher clinical success rate in the PP population 14 days post-therapy compared to cefuroxime axetil (96.7% vs 90.7%, respectively, 95% CI, 1.5%; 10.6%) as well as a statistically higher bacteriological success rate (94.5% vs 83.5%, 95% CI, 3.6%; 19.7%). In another study, moxifloxacin resolved symptoms in significantly more patients by day 3 than amoxicillin/clavulanate (24% vs 14%, respectively, $p<0.02$) (Rakkar et al, 2001). The efficacy and safety of 7-day oral moxifloxacin (400 mg/day, n = 258) was evaluated in a multi-center, prospective study for treatment of acute maxillary sinusitis after first-line treatment failure, and acute sinusitis with high risk of complications (Gehanno et al, 2003). This study showed that patients receiving moxifloxacin had effective bacterial eradication (96%) and fast symptom relief after 3-4 days of therapy. See Table 1.2.2.3 for moxifloxacin clinical response rates during this trial.

Table 1.2.2.3. Clinical Response Rates (Gehanno et al, 2003)

	Intent-to-treat population	Per protocol population
Day 3-4		
Improvement	93.3% (238/255)	94.9% (205/216)
Failure	2.4% (6/255)	2.8% (6/216)
Indeterminate response/missing data	4.3% (11/255)	2.3% (5/216)
7-10 days post-treatment		
Clinical success or complete resolution of signs/symptoms	90.2% (230/255)	92.6% (200/216)
Failure*	7.1% (18/255)	7.4% (16/216)
Indeterminate response/missing data	2.7% (7/255)	0
4-5 weeks post-treatment[ϒ]		
Continued resolution	98.3% (226/230)	99.0% (198/200)
Relapse	1.3% (3/230)	1.0% (2/200)
Missing data	0.4% (1/230)	0

* Failures occurring during treatment are included.

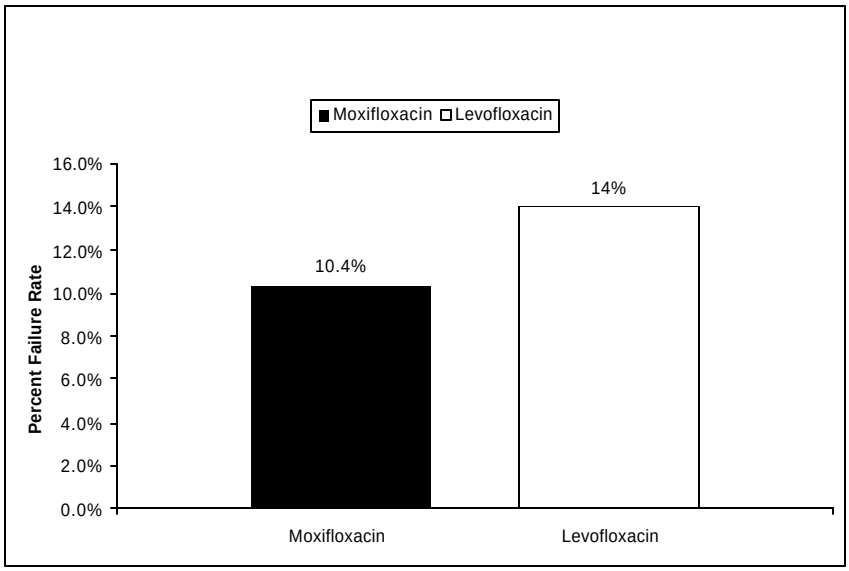
[ϒ]In patients considered resolved at 7-10 days post-treatment.

A retrospective study was conducted to evaluate how differences in labeled recommendations for duration of antibiotic therapy for the treatment of acute sinusitis translate into practices, outcomes and costs in the real world (Data on File, Schering-Plough Corporation). Data for this study, which included 3358 acute sinusitis episodes with moxifloxacin as initial therapy and 1522 episodes with levofloxacin as initial therapy, was obtained from the PharMetrics' database. The study was conducted between April 2000 and March 2002. Baseline characteristics were generally similar between the two groups with the exception of fewer immunocompromised patients ($p=0.003$), fewer episodes being in the emergency department ($p=0.008$) and lower log-lagged charges ($p=0.008$) in the moxifloxacin group.

Based on the claims data, the average duration of therapy was 10.4 days in the moxifloxacin group compared to 12.4 days in the levofloxacin group ($p<0.001$). There was also a significantly lower

failure rate in the moxifloxacin group than the levofloxacin group (10.4% vs. 14%, respectively, p=0.003) (see Figure 1.2.2.1 below).

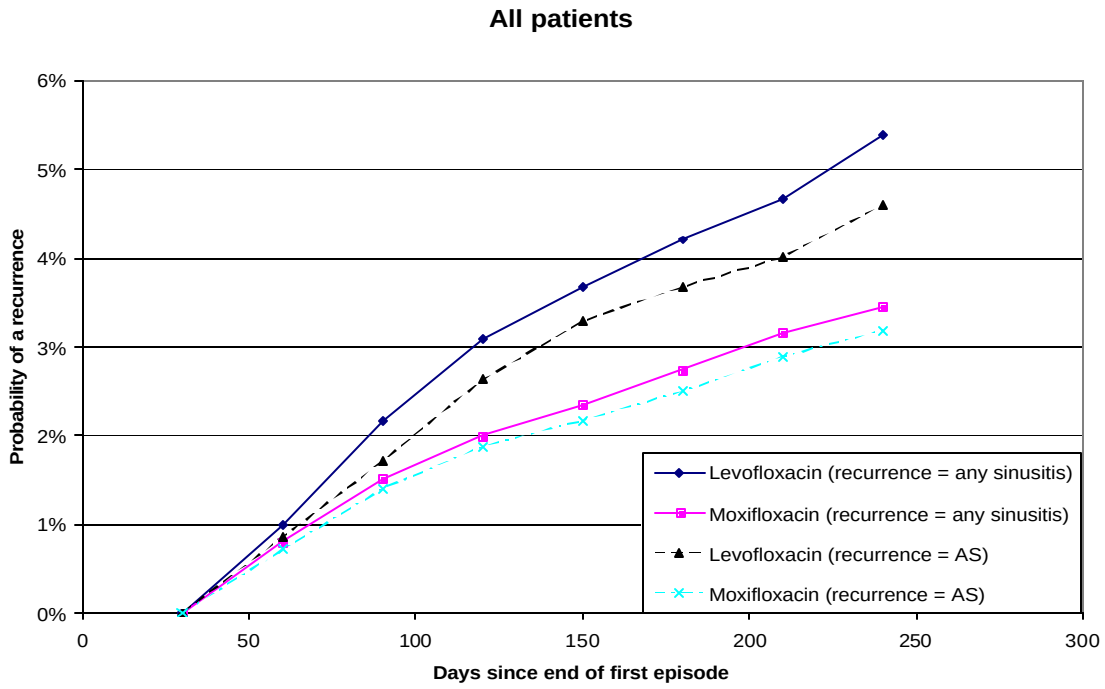
Figure 1.2.2.1. Failure Rate with Moxifloxacin and Levofloxacin in the Treatment of Acute Bacterial Sinusistis



*p=0.003

Hazard regression analysis of recurrence data demonstrated that the recurrence probability for acute sinusitis was 36% lower for moxifloxacin patients versus levofloxacin patients (p<0.0062). The graph below (Figure 1.2.2.2) shows the probability of recurrence of acute sinusitis and any sinusitis episode over time for moxifloxacin and levofloxacin. Finally, the moxifloxacin initiated group had lower average treatment charges ($171 vs. $211, p=0.03) and average pharmacy charges ($103 vs. $117, p<0.0001) compared to the levofloxacin group (costs were adjusted to 2002 dollars using the Consumer Price Index).

Figure 1.2.2.2. Probability of Recurrence for Acute Sinusistis or Any Sinusitis for Moxifloxacin Compared to Levofloxacin



AS – acute sinusitis

1.2.2.g Expected Outcomes of Therapy

When treating acute bacterial sinusitis with antibiotic therapy, the primary goal is to control the infection, but three other therapeutic goals should also be considered – reduction of tissue edema, facilitation of drainage, and maintenance of potency of the sinus ostia. (Stafford, 1990). Studies have shown that 80 to 90% of patients experience symptomatic and bacteriologic improvement within 7 to 14 days of antibiotic therapy (Fagnan, 1998).

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1.2.3 Acute Bacterial Exacerbations of Chronic Bronchitis (ABECB)

Summary

Patients with chronic bronchitis often have poor baseline functional status with few respiratory reserves. Infections can worsen their condition and lead to a quick decline in pulmonary function. Bacterial infection is implicated in approximately 40% to 50% of ABECB based on microbiological testing (Sethi et al, 2000). Empirical antibiotic treatment of ABECB in patients with a range of different conditions has become widely accepted as standard practice, especially in patients who present with increased dyspnea, sputum volume, and purulent sputum. The evidence that bacteria cause exacerbations, which contribute to loss of lung function, has emphasized the importance of appropriate antibiotic treatment of acute exacerbations. A useful agent in treatment of ABECB would be rapidly bactericidal and increase the time in between exacerbations without requiring additional treatment. Moxifloxacin has demonstrated effectiveness as short-course therapy for bacterial ABECB in an extensive clinical program comprising comparative studies with various standard antimicrobials (Wilson et al, 1999, Wilson et al, 2004). Moxifloxacin rapidly penetrates the site of infection in bacterial ABECB within the first 3 hours and concentrates there to levels well exceeding the MIC_{90}s of common respiratory tract pathogens (Avelox PI). Moxifloxacin has targeted *in vitro*[*] bactericidal activity, offers once daily dosing, and is indicated for a short 5-day course of therapy for the treatment of ABECB.

1.2.3.a Epidemiology and relevant risk factors

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder largely caused by smoking, which is characterized by progressive, partially reversible airway obstruction, systemic manifestations, and increasing frequency and severity of exacerbations (Pauwels et al, 2001). Approximately 20% of adult Americans have COPD. Despite public education about the dangers of smoking, COPD continues to be a major medical problem and is now the fourth leading cause of death in the United States (NHLBI, 2003). The cost of COPD to the nation in 2002 was estimated to be $32.1 billion (NHLBI, 2003). Acute bronchitis and acute exacerbations of COPD are among the most common illnesses encountered by family physicians and account for more than 16 million physician visits annually (McCrory et al, 2001). A problem common to all patients with COPD, regardless of disease severity, is ABECB, with some or all of the cardinal symptoms of increased dyspnea, increased sputum volume, and increased sputum purulence. Acute exacerbations are the most frequent cause of medical visits, hospital admissions, and death among patients with COPD. In addition, frequent exacerbations are an important determinant of quality-of-life measures in this group of patients and contribute to accelerated rates of decline in lung function. The average COPD patient experiences two to three exacerbations per year, and patients with a lower FEV_1 have more frequent exacerbations. Treatment for exacerbation remains controversial. At least one half of the cases of ABECB are thought to be infectious in nature. Some authors suggest that acute exacerbation is non-infectious in nature and does not require treatment, citing triggering factors for exacerbations that include congestive heart failure and exposure to allergens and irritants (i.e., cigarette smoke, dust, cold air, or pollutants). Other studies have shown that treating ABECB with an antibiotic decreases the duration of illness and improves peak flow measurements.

The primary risk factor for COPD and chronic bronchitis is smoking. Other underlying conditions that predispose patients to COPD include air pollution and occupational exposure to dust, gas, or fumes. A number of pathologic mechanisms have been identified which predispose patients with COPD and chronic bronchitis to infection. These include histologic abnormalities found among

[*] The clinical relevance of *in vitro* data is not known.

patients with COPD, which may enhance the development of pulmonary infection. Host immune defects and the presence of increased proinflammatory molecules in patients with COPD may lead to an abnormal inflammatory airway response following a minor insult (DiStefano et al, 1994). Acquisition of a new strain of bacteria may also predispose the patient to infection (Sethi et al, 2002). Acute exacerbations are also associated with environmental exposures such as second hand smoke, air pollution, allergens, occupational exposure, and/or subclinical asthma.

1.2.3.b Pathophysiology and Microbiology

The pathologic hallmark of chronic bronchitis is an increase in goblet cell size and number that leads to the excessive mucus secretion. Hypertrophy of the submucosal glands in the walls of the large bronchi may occur early in chronic bronchitis due primarily to prolonged exposure to cigarette smoke. The resulting mucous hypersecretion later involves the small airways and may be associated with replacement of the ciliated respiratory epithelium with non-ciliated, metaplastic or goblet cells. These abnormalities lead to impaired clearance and chronic low-grade inflammation, even in the absence of infection.

ABECB can result from viral infections of the upper airways, bacteria, or non-infectious causes. Controversy exists regarding the nature of the infectious agent(s) in ABECB, as well as their exact role. A causative role of bacteria in some exacerbations of obstructive lung disease has been suggested, although 25%-30% of cases are usually caused by viruses, and patients may have more than one organism present or additional organisms presenting later in the disease (Miravitlles et al, 1999, Sethi et al, 2000). When bacteria are involved, the most common causative agents are *Haemophilus influenzae* (60%), *Streptococcus pneumoniae* (15%), *Moraxella catarrhalis* (15%), and *Chlamydia pneumoniae* (5%) (Lode et al, 2002).

1.2.3.c Clinical Presentation

COPD is defined as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema. The most common symptoms and signs include cough, dyspnea on exertion, and increased phlegm production. Additional signs and symptoms include wheezing, prolonged expiration with pursed lip breathing, barrel chest, use of accessory muscles of breathing; and in advanced cases cyanosis, evidence of right heart failure, and peripheral edema. Most patients with COPD have stage 1 disease, according to the American Thoracic Society, which means their forced expiratory volume in 1 second (FEV_1) is at least 50% of the predicted value. Stage 2 is defined as an FEV_1 value of 35%-49% of the predicted value, and stage 3 is defined as an FEV_1 value of less than 35% of the predicted value. Chronic bronchitis is defined as the presence of chronic productive cough for 3 months in each of two successive years in a patient in whom other causes of chronic cough have been excluded (American Thoracic Society, 1995).

Patients with ABECB experience a sudden onset of increased mucus thickness and purulence along with shortness of breath, causing congestion and making it difficult for the lungs to clear harmful bacteria. The clinical features of ABECB are:

- Increased volume or change in the character of sputum;
- Increased frequency and severity of cough;
- Increased dyspnea;
- Variable constitutional symptoms;
- Unchanged chest radiograph;
- Variable decrease in pulmonary function (FEV_1 and vital capacity);
- Respiratory rate > 25/min.

Complicated ABECB is identified clinically as significant impairment of lung function ($FEV_1 \leq 50\%$ of predicted), frequent exacerbations (4 or more per year), lengthy duration of disease, significant comorbidity, use of supplemental oxygen, and use of chronic oral corticosteroid.

1.2.3.d Approaches to Treatment – Principal Options/Practice Patterns

In a grading system for the severity of an acute exacerbation, patients are stratified by exacerbation characteristics: increased sputum volume, increased sputum purulence, and increased dyspnea over baseline (Anthonisen et al, 1987, O'Donnell et al, 2003). Anthonisen Type 1 is the most severe and includes the presence of all 3 of these symptoms; Anthonisen Type 2, 2 of 3 symptoms are present; Anthonisen Type 3, 1 of 3 symptoms are present (plus an upper respiratory tract infection in the previous 5 days, increased wheezing, increased cough, fever without an obvious source, or a 20% increase in respiratory rate or heart rate above baseline). Antimicrobial therapy is warranted for patients with ABECB if they fall into the Anthonisen type 1 or type 2 categories. The choice of agent to treat an infectious exacerbation is dependent on the suspected pathogen and patterns of local resistance. A narrow-spectrum antibiotic (eg, amoxicillin, trimethoprim/sulfamethoxazole, doxycycline, etc.) is the recommended first-line therapy (McCrory et al, 2001, Anthonisen et al, 1987). Because *Streptococcus pneumoniae* and *Haemophilus influenzae* resistance has increased, selected 2nd or 3rd generation cephalosporins or a 2nd generation macrolide may be a treatment choice; however, if patients fail treatment, alternative therapies such as a β-lactam/β-lactamase inhibitor or a fluoroquinolone is recommended as an alternative treatment. Fluoroquinolones or amoxicillin/clavulanate are recommended for complicated ABECB patients. The recommendation of the American College of Physicians (ACP) is to restrict antibiotic treatment to those with "severe exacerbations" (Snow et al, 2001). Patients with complicated ABECB have risk factors that have been associated with an increased likelihood of treatment failure and/or infection with more virulent or resistant organisms. As a result, antibiotics with enhanced antimicrobial coverage are recommended. Fluoroquinolones have been shown to have enhanced eradication of potentially pathogenic bacteria compared with extended-spectrum macrolides (Wilson et al, 1999, Chodosh et al, 1998) or aminopenicillins and cephalosporins (Wilson et al, 2004). Fluoroquinolones are used in practice for the treatment of bacterial ABECB because of their high serum levels with oral administration and because of increasing antibiotic resistance of other agents against pathogens such as *Streptococcus pneumoniae*. Fluoroquinolone treatment may lead to longer infection-free intervals, suggesting they may be a better choice for the treatment of infections in COPD patients with multiple risk factors or frequent exacerbations. It is recommended that if a patient requires repeated antibiotic therapy within a 3-month period, a different class of antibiotics should be used to avoid the increased risk of developing resistance.

1.2.3.e Alternative Treatments

Adjunctive, non-antibiotic therapies for patients with ABECB are smoking cessation, some bronchodilators, oxygen, oral corticosteroids, rehabilitation, and nutritional programs. To control chronic bronchitis including ABECB, sources of irritation and infection in the nose, throat, mouth, sinuses, and bronchial tubes must be eliminated. Polluted air and dusty working conditions should be avoided.

1.2.3.f Place of Moxifloxacin Therapy in Treatment

Important changes have been occurring in the epidemiology and resistance patterns for antibiotics used as first-line therapy in patients with bacterial ABECB. The increasing prevalence of penicillin non-susceptible isolates of *Streptococcus pneumoniae* is a problem in the United States. Recent surveillance data suggest resistance of *Streptococcus pneumonia* isolates to the macrolides is increasing (Bozdogan, Appelbaum, 2004). Fluoroquinolones are increasingly being used as empiric therapy for the management of community-acquired respiratory tract infections, in part because of the prevalent resistance to more traditional agents, but also because of their targeted spectrum of activity. Moxifloxacin achieves drug concentrations at least three times higher in lung tissues than the older fluoroquinolones levofloxacin and ciprofloxacin (Mandell et al, 2004). Moxifloxacin rapidly penetrates the site of infection in the bronchial mucosa and alveolar macrophages within the first 3 hours after administration and concentrates there to levels well exceeding the MIC_{90}s of common respiratory tract pathogens (Avelox PI).

Clinical studies support the use of moxifloxacin in bacterial ABECB. Short course (5-day) moxifloxacin (400 mg QD) showed superior bacterial eradication rates when compared to a 7 day course of clarithromycin (500 mg BID) at both 7 days and 14 days (95% CI 8.5%, 27.7% and 3.6%, 26.9%, respectively) in a prospective, randomized clinical trial (Wilson et al, 1999). In a multi-national, randomized, double-blind study, the efficacy and safety of a 5-day course of moxifloxacin (400 mg QD) was compared with standard oral 7-day b.i.d. and t.i.d. antibiotic treatment regimens (n = 319) as first-line therapy for infectious ABECB (Wilson et al, 2004). This study demonstrated that moxifloxacin was equivalent to the comparator regimen for the primary outcome measure, i.e., clinical success at 7 to 10 days after therapy, and superiority with moxifloxacin was shown for both short-term and long-term efficacy variables including cure rate (defined as retun to pre-exacerbation status, no additional antimicrobial therapy required), need for additional antimicrobial treatment of ABECB, rate of bacteriologic eradication, and time to next exacerbation. Moxifloxacin treated patients less frequently required additional antibiotic therapy compared to the comparator in the PP population ($p=0.045$) as well as the ITT population ($p=0.006$) and experienced more time between exacerbations ($p=0.03$). In addition, a significantly higher proportion of moxifloxacin patients, receiving no concomitant steroid therapy or with no change in existing steroid regimen, reported clinical cure in the ITT population ($p=0.03$). Trial design and clinical success rates (defined as clinical cure, return to pre-exacerbation status, and clinical improvement, not complete return to pre-exacerbation stutus, but sufficient improvement in clinical singns and symptoms that no alternative antimicrobial therapy was required) for the Wilson trial are depicted in the following tables (Tables 1.2.3.1 and 1.2.3.2.)

Table 1.2.3.1. Trial Design (Wilson et al. 2004)

Trial Design	Inclusion Criteria	Exclusion Criteria
Randomized, double-blind study of 2 parallel treatment arms	Outpatients aged ≥ 45 years with documented chronic bronchitis (CB) were eligible for enrollment during an ABECB-free period if they had: • A history of cigarette smoking of at least 20 packs/year • Two or more documented ABECB in the previous year • FEV_1 < 85% of predicted value at enrollment visit (FEV_1: forced expiratory volume in the first second)	• Previous adverse reaction to study drugs • Pregnancy or lactation • Syndrome of QTc prolongation • Severe renal or hepatic impairment • Lung disease other than CB that could affect the clinical evaluation of study medication

Treatment and Dosage Regimens	Criteria for Evaluation
Moxifloxacin 400 mg q.d. 5 days **Comparator** amoxicillin 500 mg t.i.d. 7 days, OR clarithromycin 500 mg b.i.d. 7 days, OR cefuroxime axetil 250 mg b.i.d. 7 days	***Efficacy*** • **Primary** – Clinical response 7-10 days post-therapy • **Other** ▪ Further antimicrobial use ▪ Time to next ABECB ▪ Bacteriological success ***Safety*** Clinical adverse events

Table 1.2.3.2. Clinical Efficacy Results (Wilson et al. 2004)

Clinical Efficacy Results (7-10 Days Post-Therapy)						
	ITT Population			PP Population		
	Moxifloxacin No./n (%)	Comparator No./n (%)	95% CI	Moxifloxacin No./n (%)	Comparator No./n (%)	95% CI
Clinical success[a,b]	310/354 (87.6)	312/376 (83.0)	(-0.7, 9.5)	239/274 (87.2)	251/298 (84.2)	(-3.0, 8.5)
Clinical cure	251/354 (70.9)	236/376 (62.8)	(1.4, 14.9)	191/274 (69.7)	185/298 (62.1)	(0.3, 15.6)
Clinical success w/bact confirmed ABECB[a]	98/112 (87.5)	94/120 (78.3)	(-1.4,17.9)	62/71 (87.3)	66/79 (83.5)	(-7.2,15.4)

Additional Significant Outcomes of Trial:

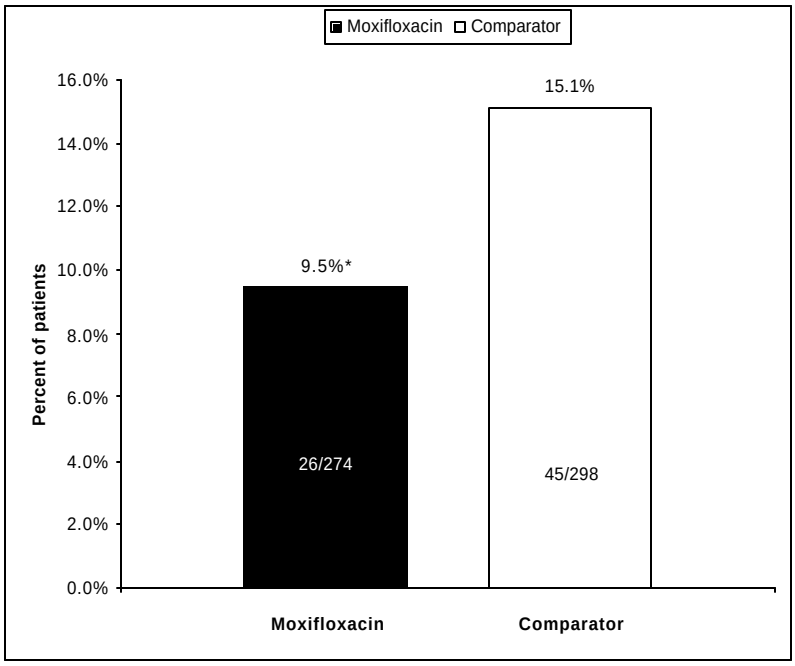
- The moxifloxacin group had a significantly lower frequency of additional antibiotic therapy than the comparator arm in the PP (p=0.045) and ITT (p=0.006) populations.
- The mean time to the next acute exacerbation of acute bronchitis was significantly lower in the moxifloxacin group than the comparator arm (p=0.03).
- A significantly higher proportion of moxifloxacin patients, receiving no concomitant steroid therapy or with no change in existing steroid regimen, reported clinical cure in the ITT population (p=0.03).

ITT - Valid for safety population
PP – Valid for efficacy population

[a]Clinical cure and improvement combined.

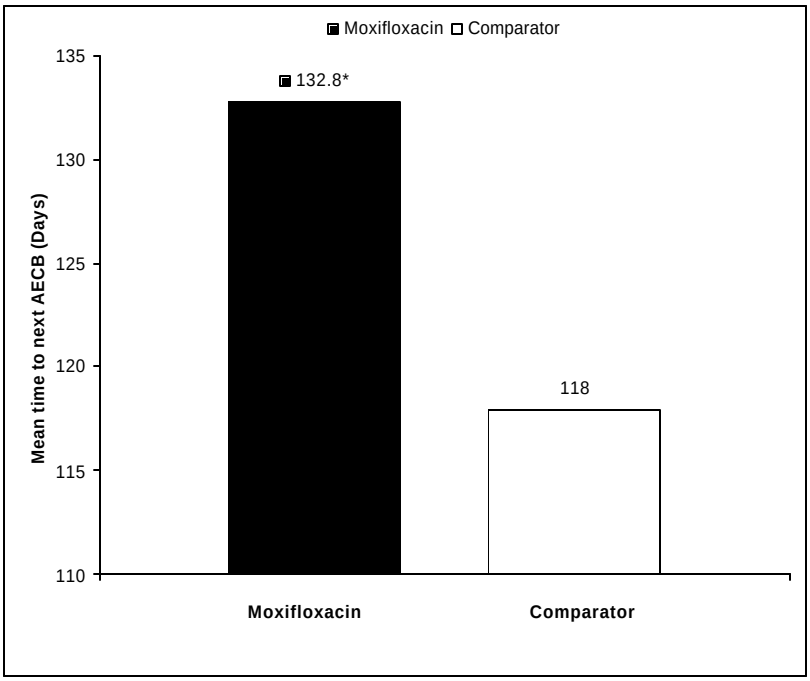
[b] In ITT population clinical success rates in amoxicillin, clarithromycin, and cefuroxime axetil groups were, respectively, 83.0%, 84.2%, 82.2%; in per-protocol population corresponding figures were 81.5%, 87.4%, and 83.8%.

Figure 1.2.3.1. Patients Requiring Additional Antibiotic Therapy (PP population)



*p=0.045

Figure 1.2.3.2. Mean Time to the Next AECB (ITT population)



* p = 0.03

In an open, community-based study of 5737 patients enrolled by more than 2000 primary care physicians from across Spain, the clinical effect of oral moxifloxacin on patients' signs and symptoms of bacterial ABECB over a 45-day period were examined. In this study, 96% of patients reported symptom relief by day 5 (Miravitlles et al, 2001).

Clinical studies demonstrate the success of moxifloxacin in bacterial ABECB. Moxifloxacin is convenient to use in both the community and the hospital setting and has a proven safety and tolerability record.

1.2.3.g The Expected Outcomes of Therapy – Resolution of Symptoms

Resolution of symptoms of ABECB include decreased volume and clearing color of sputum, improved cough, decreased dyspnea, and improved spirometry. Antibiotic therapy is administered in patients with ABECB because of a suspected bacterial pathogen and to shorten the duration of the exacerbation. The normal course of an ABECB will vary depending on the severity of the underlying disease, but patients often begin to improve after three or more days of therapy.

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1.2.4 Skin and Skin Structure Infections (Uncomplicated and Complicated)

Summary

Bacterial infections of the skin and underlying skin structure are common presentations in patients visiting emergency room clinics and office-based practices. Severity of infection can range from uncomplicated skin and skin structure infections such as superficial skin infections, impetigo, erysipelas, cellulitis, and simple abscesses to more complicated infections including diabetic foot infections, post surgical wound infections, fascitis, or infected ischemic ulcers. These infections are typically diagnosed by clinical presentation and treated empirically. Antimicrobial therapy is beneficial for both recovery from these infections and preventing disease progression. To be effective, an antimicrobial agent has to be present in high concentrations relative to the minimum inhibitory concentration (MIC_{90}) of the susceptible pathogens at the site of infection as well as provide coverage for a broad spectrum of pathogens.

Moxifloxacin attains good penetration into peripheral tissues, with concentrations often exceeding plasma concentrations, including subcutaneous tissue, skeletal muscle, skin blister fluids, and inflammatory fluids. Moxifloxacin has targeted *in vitro*[*] activity and proven clinical efficacy against *Staphylococcus aureus* and *Streptococcus pyogenes*, the most common causes of uncomplicated skin and skin structure infections. Moxifloxacin is a broad spectrum fluoroquinolone which has also demonstrated *in vitro*[*] activity against aerobic gram negative and anaerobic bacteria (Avelox PI), commonly associated with complicated skin and skin structure infections. In addition to proven clinical efficacy in the treatment of uncomplicated and complicated skin and skin structure infections (Parish et al, 2000; Data on File), moxifloxacin provides convenient once daily, monotherapy treatment that does not require dosage adjustment upon change in route of administration from IV to PO. Nor does moxifloxacin require dosage adjustment in patients with renal or hepatic impairment, an important factor when treating diabetic patients, as diabetes is a co-morbidity commonly identified in patients with complicated skin and skin structure infections.

1.2.4.a Epidemiology and Relevant Risk Factors

Infections of the skin and soft tissues are among the most common types of acute infectious illness encountered in physician practices. Immunocompetent persons with no predisposing conditions may develop skin and skin structure infections. The most common community-acquired uncomplicated skin and skin structure infections (uSSSIs) include cellulitis, folliculitis, furuncles and carbuncles, wound infections, abscesses, impetigo, and erysipelas (Stulberg, 2002). Complicated skin and skin structure infections (cSSSIs) are generally identified as serious, complex infections involving deeper soft tissues that require surgical intervention and antimicrobial therapy. Infection in patients with significant underlying disease that would complicate their response to treatment (eg. diabetes mellitus, vascular disorders) may also be classified as cSSSI (FDA Guidelines, 1998).

Patients at particularly high risk of developing SSSI include those with diabetes mellitus, arterial insufficiency, venous stasis, sensory neuropathies, poor hygiene, lymphedema, intravenous drug use, immunodeficiency, presence of a foreign body, cancer, recent trauma or surgery, or obesity. Geriatric patients are at increased risk of skin infections because of age-related changes in skin, a decline in sweat gland function, dryness, and diminished response to trauma (O'Donnell, Hofmann, 2001, DiNubile, 2004).

[*] The clinical relevance of *in vitro* data is not known.

1.2.4.b Pathophysiology and Microbiology

Skin and skin structure infections generally refer to infections involving the stratum corneum, epidermis, dermis, and subcutaneous tissue. Epidermis is the outermost and avascular layer of the skin and is proliferative. The dermis contains vascular connective tissue, fibroblasts, eccrine sweat glands, and hair follicle origination. The subcutaneous tissue consists of a network of collagen and fat cells and helps conserve the body's heat while protecting other organs from injury by acting as a cushion or "shock absorber."

Infections usually occur following a break in the intact mechanical defenses of the skin that allows bacteria or other microorganisms to enter the skin or subcutaneous tissues. Cellulitis is an infection of the dermis and subcutaneous tissue with poorly defined borders commonly caused by *Staphylococcus aureus* and group A streptococci. Erysipelas is a superficial form of cellulitis involving the lymphatics with sharply defined borders almost exclusively caused by *Streptococci* spp. Impetigo is a superficial infection of the skin characterized by small, pustular vesicles that easily rupture forming a crust. Impetigo can also present in the bullous form, characterized by bullae containing clear yellow fluid that easily rupture and results in exfoliation of the skin. An abscess is a tender, erythematous, firm or fluctuant (exhibiting wave-like motion on palpation) mass of walled-off purulent material. Folliculitis is an inflammation of the hair follicles, most commonly caused by *Staphylococcus* spp. Furuncles (painful nodules in the skin circumscribed by inflammation) develop from folliculitis and involve deeper layers of skin. Carbuncles (a cluster of furuncles) extend into the subcutaneous fat tissue and are larger, more serious lesions. All of these infections are typically diagnosed by clinical presentation and treated empirically (Lewis, 1998; Stulberg et al, 2002).

For SSSI, the most frequently isolated microorganisms are *Staphylococcus aureus* and *Streptococcus*, sp., especially *Streptococcus pyogenes* (FDA Guidelines, 1998). Other commonly implicated microorganisms include Gram-negative organisms such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* spp., or *Proteus mirabilis*; other streptococci such as *Streptococcus pneumoniae* or *Peptostreptococcus* spp.; Gram-positive bacilli and other anaerobic bacteria such as *Bacteroides fragilis* (Deery, 1998; Colsky et al, 1998).

1.2.4.c Clinical Presentation

Skin infections classically present with pain, erythema, warmth, swelling, and tenderness. Induration, fluctuance, and crusting or drainage may also be present. Skin and skin structures from any site may be affected, but involvement of the lower extremities is common, especially in elderly patients. More severe and sometimes even life-threatening infections are characterized by evidence of spreading or deep infection as is seen in erysipelas or lymphangitis. Purplish discoloration, skin necrosis, crepitans, or blistering should raise the clinician's suspicions for more severe infections such as a deep abscess, fascitis, or other necrotizing process. Fever and leukocytosis are frequently, but not invariably, present.

1.2.4.d Approaches to Treatment

A precise microbiologic diagnosis is made in < 20% of cases of SSSI (Deery, 1998). Therefore, the choice of antimicrobial agents for treatment of skin infections is usually empiric and is directed against the most likely causative agents. The pattern of bacterial resistance to antimicrobial agents in the community may also dictate which agents are used. Currently, the classes of antibacterial agents used in uSSSI include penicillins, extended-spectrum penicillin derivatives and β-lactamase inhibitors, cephalosporins, clindamycin, carbapenems, and fluoroquinolones. Cephalosporins, such as cephalexin, are the most commonly used antibiotics in North America for outpatient treatment of

skin and soft tissue infections (Wilson, 1998). Such agents have the advantages of being inexpensive, well tolerated, and quite effective. However, streptococci and *Staphylococcus aureus* have shown increasing resistance trends to β-lactams and other antimicrobials (Bozdogan, Appelbaum, 2004). Fluoroquinolones are potent broad-spectrum antimicrobial agents, with the older agents having broad-spectrum anti-Gram-negative activity, borderline activity against clinically important Gram-positive pathogens, and little or no anti-anaerobic bacteria activity. In contrast, the new quinolones such as moxifloxacin have enhanced activity against Gram-positive pathogens, and they remain highly active against aerobic Gram-negative bacilli. It may be necessary to use some fluoroquinolones in combination with anti-anaerobic agents for those infections with mixed aerobic and anaerobic pathogens (Blondeau, 2002). Fluoroquinolones are particularly effective in the treatment of SSSI not only because of their broad spectrum of activity against microorganisms that cause skin infections, but also because of their excellent penetration into peripheral tissues (Blondeau, 2002; Karchmer, 1999).

1.2.4.e Alternative Treatment Options

β-Lactamase-stable penicillins such as oxacillin and amoxicillin/clavulanate may be successfully used to treat most skin and soft tissue infections caused by staphylococci or streptococci. Additionally, the broad activity of amoxicillin/clavulanate makes it especially useful when a polymicrobial infection is suspected, such as in infections that follow animal bites. The newer macrolides such as azithromycin and clarithromycin also may be used to successfully treat skin infections, although the failure rate may be somewhat higher than when such infections are treated with cephalexin.

1.2.4.f Place of Moxifloxacin in Treatment

With multi-drug-resistant strains of bacteria emerging and widespread cross-resistance to antibiotics, the treatment of SSSI can be increasingly challenging. There is no known cross-resistance between moxifloxacin and other classes of antimicrobials. Moxifloxacin's chemical structure contributes to a lower selection of resistant mutants and prevents active efflux in Gram-positive bacteria (Avelox PI). A number of antimicrobial therapies, including agents in the fluoroquinolone class, have received an indication for the treatment of SSSI during the past several years. Moxifloxacin provides targeted activity against Gram-positive pathogens commonly causing skin infections such as *Staphylococcus aureus* and *Streptococcus pyogenes,* in addition to Gram-negative aerobic pathogens, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*. Moxifloxacin has also shown *in vitro*[*] activity against anaerobes, including *Fusobacterium* sp., *Peptostreptococcus* sp., and *Prevotella* sp (Avelox PI). Rapid penetration of moxifloxacin into the tissue and blister fluids was observed in a pharmacokinetic study. Moxifloxacin was administered in healthy volunteers either via the oral or IV route and mean maximum concentration in the plasma and inflammatory fluid were similar after oral and IV dosing. In this study, moxifloxacin attained peak concentration levels in blister fluid in as soon as 3.86 hours and maintained drug levels above MIC_{90} values for both *S. aureus* and *S. pyogenes* (Wise et al, 1999; Blondeau et al, 2000).[*] Moxifloxacin's broad spectrum of activity and rapid penetration makes it a strong candidate for the empiric treatment of SSSIs.

Clinical studies support the use of moxifloxacin in SSSI. A U.S. prospective, randomized, multi-center, double-blind trial (N = 401) compared the efficacy and safety of 7-day Avelox 400 mg once daily and cephalexin 500 mg three times daily in patients with uSSSI (Parish et al, 2000). The clinical response rates and bacterial eradication rates were excellent, and similar in both treatment

[*] The clinical relevance of *in vitro* activity is not known.

[*] Although tissue/fluid penetration is important, penetration levels do not necessarily correlate with clinical effectiveness.

groups. In addition, moxifloxacin treatment was associated with excellent clinical outcomes in patients over 65 years, and in wound infection (Parish et al, 2000). The adjusted mean duration of the initial prescription for treating a uSSSI was studied using medical claims data (n = 1896), and was approximately 1 day shorter for patients treated with moxifloxacin than for those treated with levofloxacin ($P < 0.01$) (Keating et al, 2004).

Two Phase III, prospective, comparative, multi-center studies were conducted to compare the activity of intravenous (IV)/oral (PO) moxifloxacin to an IV/PO beta-lactam/beta-lactamase inhibitor for the treatment of cSSSI (Data on File). There was no statistical difference in the clinical and bacteriological response rates for moxifloxacin when compared to either piperacillin/tazobactam or amoxicillin/clavulanate. In both studies, the most frequently isolated pathogen was *Staphylococcus aureus*. Overall, the incidence of adverse events in these studies was comparable between treatment arms with the exception of gastrointestinal side effects, which have been reported with a higher incidence in the moxifloxacin treated groups. The severity of most of the adverse events reported was mild to moderate in severity.

Unlike many other quinolones, photosensitivity is not a major problem associated with administration of moxifloxacin. Moxifloxacin will not interfere with co-administration of other medications that are metabolized by the cytochrome P-450 system (e.g., digoxin, theophylline, warfarin). Moxifloxacin can be conveniently transitioned from IV to PO without dosage adjustment and offers once daily dosing (Avelox PI).

1.2.4.g Expected Outcome of Therapy

The treatment of skin and skin structure infections should result in resolution of all signs and symptoms and eradication of the pathogenic organism. The treatment of complicated skin and skin structure generally requires surgical intervention in addition to requiring antimicrobial therapy with a broad spectrum antibiotic.

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Section 2.
Supporting Clinical and Economic Information

2.1 Presenting Clinical Study Results

2.1.a Pivotal Safety and Efficacy Trials

Summaries of the following pivotal safety and efficacy trials are contained in this subsection:

File TM Jr, Larsen LS, Fogarty CM, et al. Safety and efficacy of sequential (IV to PO) moxifloxacin for the treatment of community-acquired pneumonia in hospitalized patients. *Today's Ther Trends*. 2001;19(4):251-70.

Finch R, Schürmann D, Collins O, et al. Randomized controlled trial of sequential intravenous (i.v.) and oral moxifloxacin compared with sequential i.v. and oral co-amoxiclav with or without clarithromycin in patients with community-acquired pneumonia requiring initial parenteral treatment. *Antimicrob Agents Chemother*. 2002;46(6):1746-54.

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Section 2.1.a.1
Pivotal Safety and Efficacy Trials Community-Acquired Pneumonia

Citation: File TM Jr, Larsen LS, Fogarty CM, et al. Safety and efficacy of sequential (IV to PO) moxifloxacin for the treatment of community-acquired pneumonia in hospitalized patients. *Today's Ther Trends*. 2001;19(4):251-270.

Trial Design	Inclusion Criteria	Exclusion Criteria
Prospective, randomized, double-blind, double-dummy	• Subjects ≥ 18 years with mild to moderate or severe CAP requiring IV therapy • Patients having fever (≥ 38°C [oral]; > 38.5°C [tympanic]; or > 39°C [rectal]) and/or elevated white blood cell count (WBC) count (≥ 12,000/mm^3), total WBC count < 4500/mm^3, or ≥ 15% immature neutrophils • At least one of the following: productive cough, purulent sputum, dyspnea, or tachypnea [> 20 breaths/min], rigor/chills, pleuritic chest pain, or signs of pulmonary consolidation • New or progressive infiltrate on chest x-ray confirmed by radiologist	Nursing home residents, pregnancy/lactation, those hospitalized for > 48 hours at the time of pneumonia diagnosis, pre-therapy APACHE II score > 30, known bronchial obstruction or history of post-obstructive pneumonia, previous therapy with systemic antibiotic for > 24 hours prior to enrollment unless a failure with isolated pathogen, requirement for concomitant antibacterial therapy with similar spectrum, moderate to severe liver or renal impairment, allergy to fluoroquinolones, allergy to multivitamin infusion or pre-existing hypervitaminosis, history of fluoroquinolone tendinopathy; history of prolonged QTc interval, use of Class IA or III antiarrhythmics, or uncorrected hypokalemia, absolute neutrophil count < 1000 cells/mm^3 or significant immunosuppression, rapidly fatal underlying disease, and any coexistent disease which could affect study outcome

Sample Characteristics – No. of Patients

	Moxifloxacin	Comparator	Total
Randomized	253	263	516
ITT	249 (98%)	258 (98%)	507
Clinically Valid	177 (70%)	179 (68%)	356
Valid for Microbiology	75 (30%)	77 (29%)	152

ITT = intent to treat

Treatment and Dosage Regimens

- **Moxifloxacin** sequential IV/PO 400 mg QD
- **Comparator** initially IV alatrofloxacin/PO trovafloxacin 200 mg QD, changed to IV/PO levofloxacin 500 mg QD after concerns about hepatotoxicity

Each subject received a total of 7-14 days of IV/PO therapy

Criteria for Evaluation

Efficacy

- **Primary** - Clinical response (cure, failure, or indeterminate) at test-of-cure visit (7-30 days post-therapy)
- **Secondary** - Clinical response as related to infecting pathogen was also determined for microbiologically valid population

Safety

Assessed by clinical observation and conventional lab tests, including blood and urine samples for routine hematology, chemisty, coagulation, and urinalysis evaluation. A 12-lead ECG was performed when possible at pre-therapy, on Day 1 pre- and post-study drug infusion, and on Day 3 pre- and post-study drug infustion. AEs rated by the investigator as to their severity and relationship to the study drug

- Both Tx groups were comparable on demographic and baseline characteristics *except* more subjects in moxifloxacin group had severe CAP (34% vs 27%), more were categorized as having a poor general health status (6% vs 3%), were older, and had a higher proportion of active smokers (80% vs 74%). None of these differences reached statistical significance
- Safety and efficacy assessed prior to therapy (within 48 hours of the first dose of study drug), during therapy (time of IV/PO switch or day 3-5), at the end of the therapy at test-of-cure visit (TOC) (7-30 days post-therapy), and at late follow-up (28-42 days post-therapy)

Clinical Resolution at TOC Visit (7-30 Days Post-Tx)

	Moxifloxacin n/N (%)	Comparator n/N (%)
Safety (ITT)	168/249 (67%)	173/258 (67%)
Clinically valid*	155/177 (88%)	160/179 (89%)
Mild/moderate	107/116 (92%)	121/130 (93%)
Severe	48/61 (79%)	39/49 (80%)
Microbiologically valid	64/75 (85%)	69/77 (90%)

(*primary endpoint)

- Confidence intervals showed no statistically significant difference between treatment groups for safety, clinically valid, and microbiologically valid populations.
- Excellent correlation between bacteriological response and clinical response. In patients with eradication or presumed eradication of pre-therapy bacteria, clinical cures were observed for 57 of 58 moxifloxacin and 60 of 60 comparator treated subjects

Summary of Adverse Events (ITT Population)

Adverse Events (AEs)	Moxifloxacin (n = 249)	Comparator (n = 258)
Any drug-related AE	98/249 (39%)	103/258 (40%)
Discontinuation due to AE	24/249 (9%)	23/258 (9%)

Incidence Rates of Drug-Related AEs Occurring in ≥ 2% of Patients

Adverse Event	Moxifloxacin (n = 249)	Comparator (n =258)
Injection site reaction	13 (5%)	22 (9%)
Headache	5 (2%)	13 (5%)
Diarrhea	17 (7%)	17 (7%)
LFT abnormalities	10 (4%)	6 (2%)
Nausea	8 (3%)	13 (5%)
Oral moniliasis	7 (3%)	5 (2%)
Dyspepsia	6 (2%)	1 (< 1%)
Vomiting	3 (1%)	10 (4%)
Insomnia	8 (3%)	6 (2%)
Tremor	4 (2%)	1 (< 1%)
Dizziness	1 (<1%)	11 (4%)
Pruritus	2 (<1%)	5 (2%)
Rash	1 (<1%)	8 (3%)

- 62 % (154) of moxifloxacin treated patients and 65% (167) of comparator treated patients completed the 12-lead ECG recordings both pre- and post-study drug IV infusion on Day 3.
- Change in QT_c from pre-treatment to baseline was found to be 3 ± 28 msec for moxifloxacin and 4 ± 25 msec for the comparator.
- No QT_c prolongation-related cardiovascular morbidity or mortality was noted in either treatment group.

Citation: Finch R, Schürmann D, Collins O, et al. Randomized controlled trial of sequential intravenous (i.v.) and oral moxifloxacin compared with sequential i.v. and oral co-amoxiclav with or without clarithromycin in patients with community-acquired pneumonia requiring initial parenteral treatment. *Antimicrob Agents Chemother*. 2002;46(6):1746-1754.

Location	Trial Design	Inclusion Criteria	Exclusion Criteria
65 centers in 10 countries (Belgium, France, Germany, Greece, Israel, South Africa, Spain, Switzerland, Russia, and the United Kingdom)	Multi-national, multi-center, randomized, open, parallel-group	• Males and females aged 18 years and over with radiological evidence of CAP, in hospital < 48 hours • Having temp ≥ 38.5°C or leukocytosis and ≥ 1 of following: pneumonia including cough, purulent sputum, dyspnea, rigors, pleuritic chest pain, or auscultatory findings • All patients required initial parenteral therapy and approximately half had severe pneumonia, as defined by the criteria of the American Thoracic Society	Presence of coexisting disease considered likely to affect the outcome of the study, or a rapidly fatal underlying disease; known prolongation of the QT interval or the use of class IA or class III antiarrhythmics; known hypersensitivity to fluoroquinolones, β-lactams, or macrolides; aspiration pneumonia; and pre-treatment with systemic antibacterial agents for more than 24 hours prior to enrollment in the study. Patients failing previous antibacterial therapy, which they had received > 72 hours for the current pneumonia episode, could be enrolled unless the antibacterial regimen contained a fluoroquinolone or a β-lactam/β-lactamase inhibitor combination.

Sample Characteristics – No. of Patients

	Moxifloxacin	Comparator	Total
Enrolled	306	322	628
ITT	301 (98%)	321 (100%)	622
PP	258 (84%)	280 (87%)	538
Non-severe pneumonia	129 (50%)	143 (51.1%)	272
Severe pneumonia	129 (50%)	137 (48.9%)	266

ITT = intent to treat (valid for safety)
PP = per protocol.

Treatment and Dosage Regimens

- **Moxifloxacin** 400 mg IV QD followed by 400 mg PO for 7 to 14 days
- **Comparator** co-amoxiclav* 1.2 g IV t.i.d. followed by co-amoxiclav 625 mg PO t.i.d. with or without clarithromycin 500 mg b.i.d. (IV* or PO) for 7 to 14 days

* IV comparator is not FDA approved

Criteria for Evaluation

Efficacy

- **Primary** – Clinical response (cure, failure, or indeterminate) at test of cure (TOC) visit (5-7 days after end of therapy) in the valid per protocol population (PP)
- **Secondary** – Time to resolution of fever, bacteriological response 5 to 7 days after treatment, bacteriological and clinical responses 21 to 28 days post-treatment, duration of IV therapy, and duration of hospital admission

Safety

Assessed by incidence rate of adverse events, lab data (including hematology and blood chemistry safety profile), and ECG findings

- In the comparator treated group, 192 (60%) were treated with both co-amoxiclav and clarithromycin and 129 received co-amoxiclav alone.
- Baseline characteristics were similar between the two treatment groups.
- *S. pneumoniae* and *Haemophilus influenzae* were the most commonly identified pathogens (55.4% and 19.6%, respectively).

Efficacy Analysis in the PP Population

	Moxi (n=258)	Comp (n = 280)	%D (95% CI)
Clinical cure at TOC*	241 (93.4%)	239 (85.4%)	8.0[a] (2.9-13.2)
Clinical cure at follow-up**	216 (83.7%)	208 (74.3%)	9.4 (2.6-16.3)
Bacteriological success[b] at TOC*	60 (93.7%)	58 (81.7%)	12.1 (1.2-22.9)
Bacteriological success[b] at follow-up**	54 (84.4%)	50 (70.4%)	14.0 (0.0-28.0)

* TOC: visit 5-7 days post-treatment
** follow-up: visit days 21-28 post-therapy
[a]By test of superiority, $P = 0.004$.
[b]Eradication and presumed eradication in microbiologically valid patients.

- Patients treated with moxifloxacin showed higher clinical cure rate than patients treated with co-amoxiclav alone (85%) or co-amoxiclav together with clarithromycin (85.6%)
- Rate of clinical cure was higher (vs comparator) in the moxifloxacin group in both patients with non-severe (94.6% vs 86%) and severe pneumonia (92.2% vs 84.7%).
- Irrespective of disease severity, the mean time to resolution of fever was shorter in the moxifloxacin treated patients than the comparator treated patients.
- Moxifloxacin treated patients switched to oral therapy faster than comparator treated patients (mean ± SD duration of IV therapy for moxifloxacin treated patients was 4.02 ± 1.78 days vs 4.81 ± 2.07 days for comparator treated patients).
- The mean duration of hospital stay was shorter in the moxifloxacin treated patients when compared to the comparator treated patients (9.49 ± 7.29 and 10.41 ± 7.49, respectively).

Summary of Adverse Events (ITT Population)

Adverse Events (AEs)	Moxifloxacin (n = 301)	Comparator (n = 321)
Any drug-related AE	38.9%	38.9%
Any serious AE	38 (12.6%)	53 (16.5%)
Discontinuation due to AE	15 (5%)	13 (4%)

- During the course of study there were 26 deaths, 9 in moxifloxacin group and 17 in comparator group. Most deaths (6 in the moxifloxacin and 10 in the comparator treatment group) were related to pneumonia or underlying lung disease. The difference between treatment groups were not statistically significant.
- The most serious adverse events were related to the respiratory system, 18 (6%) in the moxifloxacin group and 25 (7.8%) in the comparator treatment group.
- Most common drug-related AEs (occurring =3%) in the moxifloxacin treated patients were abnormal LFTs, diarrhea, and nausea and in the comparator treated patients, abnormal LFTs, diarrhea, nausea, and phlebitis.
- The incidence of drug-related AEs was highest for GI tract and was similar in both groups (20.9% in moxifloxacin group and 22.1% in comparator group)
- The incidence of drug-related cardiovascular events was reported as 6.6% (20 patients) in the moxifloxacin treated group and 10% (32 patients) in the comparator treated group. Twelve patients (4.0%) treated with moxifloxacin reported having serious cardiovascular AEs compared to 20 patients (6.2%) in the comparator treated patients.
- Treatment emergent clinically significant QTc prolongation was reported in one patient treated with co-amoxiclav.
- High and low laboratory values observed were not different between the two treatment groups and none of the abnormalities observed were unexpected.

Citation: Data on File. Study 10872/MRR-00140. Schering-Plough Corporation. Kenilworth, New Jersey.

Location	Trial Design	Inclusion Criteria	Exclusion Criteria
47 centers in the US	Prospective, randomized controlled, double-blind, double-dummy, multi-center, comparative study conducted from November 2002 to April 2004	Hospitalized elderly patients (=65 years), including nursing home patients, requiring initial IV therapy that also have radiologically-confirmed evidence of a new or progressive infiltrate consistent with pneumonia and =2 of the following: productive cough with purulent or mucopurulent sputum; tracheobronchial secretions or change in character of sputum; dyspnea or tachypnea; rigors or chills; pleuritic chest pain; auscultatory findings on pulmonary examination of rales/crackles and/or evidence of pulmonary consolidation; fever or hypothermia; and white blood cell count =10,000/mm^3, or =15% immature neutrophils (bands), regardless of the peripheral WBC count or leukopenia with a total WBC count <4500/mm^3.	Hospitalization for >48 hours prior to development of pneumonia; presence of end-organ damage or shock with need for vasopressors for >4 hours at the time of study entry; need for mechanical ventilation; implanted cardiac defibrillator; significant brachycardia with heart rate <50 beats/min; system antibacterial therapy for >24 hours within 7 days of enrollment unless the patient was deemed to have therapy failure after receiving >72 hours of a non-fluoroquinolone antibiotic; mechanical endobronchial obstruction; known or suspected active tuberculosis or endemic fungal infection; neutropenia; chronic therapy (=2 weeks) with known immunosuppressant therapy; known HIV infection with a CD4 count <200/mm^3; severe hepatic insufficiency; renal impairment (measured or calculated serum creatinine <20 ml/min); uncorrected hypokalemia; known prolongation of the QT_c interval or use of Class IA or Class III antiarrhythmics; previous history of tendinopathy with quinolones; or known hypersensitivity to study medications.

Sample Characteristics – No. of Patients

	Moxifloxacin	Levofloxacin	Total
Enrolled			401
ITT	195	199	394
PP	141	140	281

ITT = intent to treat (valid for safety)
PP = per protocol.

Treatment and Dosage Regimens

- **Moxifloxacin** 400 mg IV/PO QD
- **Levofloxacin** 500 mg IV/PO QD

Both treatment groups were treated for a total of 7-14 days

Patients with documented or calculated creatinine clearance of 20-49 ml/min in the levofloxacin groups were dose adjusted and received an IV levofloxacin 500 mg loading dose followed by 250 mg QD for the total therapy duration of 7-14 days.

Moxifloxacin treated patients with reduced creatinine clearance did not require dosage adjustment.

Criteria for Evaluation

Efficacy

- **Primary** – Clinical at test of cure (TOC) visit (5-21 days post-therapy)
- **Secondary** – Clinical response at the during therapy (day 3-5) visit and bacteriologic response at the TOC visit.
- **Health resource utilization assessment** – Collected at the TOC visit and included length of hospital stay, length of stay in an intensive care unit (ICU), total days of antimicrobial therapy, and duration of IV therapy.

Safety

Assessed by incidence rate of adverse events, lab data (including blood and urine samples for hematology, chemistry, coagulation, and urinalysis). Chest X-rays were conducted at baseline and repeated at the investigators discretion.

- Demographic and baseline medical characteristics were similar for both groups.
- Patients presenting with co-morbidities such as cardiac disorders (including coronary artery disease, congestive heart failure, ischemic disorders), respiratory disorders (including bronchospasm and obstruction, parenchymal lung disorders, conditions associated with abnormal gas exchange) and diabetes mellitus, however, there was no statistical significance in the incidence of any of these co-morbidities between treatment groups.

Efficacy Analysis in the PP Population

	Moxifloxacin (n=140)	Levofloxacin (n = 141)	95% CI (p-value)
Clinical cure at TOC	92.9%	87.9%	-1.9-11.9 (P=0.2)
Clinical cure for the microbiolog. valid population	17/21 (81.0%)	23/30 (76.7%)	-0.22-0.31 (P=0.98)
Bacteriologic success at TOC*	17/21 (81.0%)	21/28 (75.0%)	- (P=0.9)

*included patients with eradication and presumed eradication
microbiolog – microbiologoically

- Significantly more moxifloxacin treated patients recovered faster clinically (by day 3-5) (97.9%) than levofloxacin treated patients (90.0%) (95% CI, 1.7-14.1; p=0.01).
- 'The mean duration of total antimicrobial therapy and mean duration of IV therapy were similar between treatment groups.
- Most patients were switched to PO therapy on day 3 or 4 (93.6% moxifloxacin vs 88.6% levofloxacin) (p=0.2).
- Total hospital stay, mean hospital stay, number of patients in the ICU, and mean stay in the ICU were not statistically significant between treatment groups.

Summary of Adverse Events (ITT Population)

Adverse Events (AEs)	Moxifloxacin (n =195)	Levofloxacin (n =199)
Treatment emergent AEs	164 (84.1%)*	146 (73.4%)
Discontinuation due to AEs	15 (7.7%)	20 (10.1%)
Serious AE	46 (23.6%)	45 (22.6%)
Death	15 (7.7%)	11 (5.5%)
Drug-related AE (all)	51 (26.2%)	45 (22.6%)

*p=0.01

- Most common serious events reported in both treatment groups were exacerbation of chronic obstructive airways disease, nosocomial pneumonia, congestive heart failure, renal insufficiency, respiratory failure, and atrial fibrillation.
- None of the deaths were judged to be drug-related but related to the patient's comorbid diseases, as determined by the investigators.

Adverse Event	Moxifloxacin (n = 195)	Levofloxacin (n = 199)
Diarrhea	11 (5.6%)	10 (5.0%)
Oral candidiasis	7 (3.6%)	7 (3.5%)
Nausea	3 (1.5%)	4 (2.0%)
Clostridium difficile infection/colitis	1 (0.5%)	6 (3.0%)
Cardiac events	2 (1.0%)	7 (3.5%)
Atrial fibrillation	0	3 (1.5%)
Ventricular tachycardia	1 (0.5%)	1 (0.5%)
Acute myocardial infarction	0	1 (0.5%)
Atrial flutter	0	1 (0.5%)
Congestive heart failure	0	1 (0.5%)
Cardio-respiratory arrest	0	1 (0.5%)
Supraventricular tachycardia	1 (0.5%)	0
Torsades de pointes	0	1 (0.5%)
Chest pain	0	1 (0.5%)
Heart rate increased	0	1 (0.5%)

- There was no clinically significant difference between treatment groups for laboratory tests or vital signs assessed.

Citation: Fogarty C, Grossman C, Williams J, et al. Efficacy and safety of moxifloxacin vs clarithromycin for community-acquired pneumonia. *Infect Med*. 1999;16:748-763.

Location	Start Date and Duration	Trial Design	Inclusion Criteria
51 centers in United States	November 1996 to May 1998 (1st patient's 1st visit to last patient's last visit)	Prospective, multi-center, randomized, double-blind	• Men or women 18 years or older with fever, elevated white blood cells (>10,000/ml), and/or leukocytosis • Signs and symptoms of pneumonia including: productive cough, purulent sputum, dyspnea or tachypnea, rigor/chills, pleuritic chest pain, and/or evidence of pulmonary consolidation • Radiological evidence of new or progressive infiltrate

Sample Characteristics – No. of Patients

	Moxifloxacin	Clarithromycin	Total
Randomized	237	237	474
ITT	237 (100%)	236 (100%)	473
PP	194 (82%)	188 (79%)	382
Valid for Microbiology	110 (46%)	104 (44%)	214

ITT = intent to treat (valid for safety),
PP = per protocol (valid for efficacy).

- In the PP population, no statistical difference between treatment groups for any of the demographic/baseline variables

Treatment and Dosage Regimens

- **Moxifloxacin** 400 mg PO QD
- **Clarithromycin** 500 mg PO b.i.d.

Both treatments given for 10 days

Criteria for Evaluation

Efficacy

- **Primary** – Overall clinical response in the PP population, including during therapy, at the end of therapy (EOT, withing 6 days of completing therapy), and at follow-up (14 to 35 days post-therapy)
- **Secondary** – Overall bacteriological response as well as clinical response at EOT.

Safety

Physical examination, ECGs (at pre-therapy visits), adverse events, and blood and urine samples were collected for lab tests such as hematology, blood chemistry, and urinalysis. Chest radiographs were conducted at baseline and at each visit until infiltrate resolution.

- In the PP population, the prevalence and severity of baseline signs and symptoms of CAP were similar between treatment groups.

Summary of Clinical Response (PP Population)

		Moxifloxacin	Clarithromycin
EOT	Resolution	97%	95%
	Failure	3%	5.0%
Follow –up	Continued Resolution	98%	99%
	Relapse	2%	1%
Overall	Resolution	95%	95%
	Failure	5%	5%

Bacteriological Response

Response	Moxifloxacin	Clarithromycin
EOT (0 to +6)	99/102 (97%)	106/110 (96%)
Continued or presumed eradication at Follow-up	106/110 (94%)	100/104 (93%)

- Bacteriological response rates similar for ITT and PP populations

Summary of Adverse Events (ITT Population)

Adverse Events (AEs)	Moxifloxacin (n = 237)	Clarithromycin (n = 236)
Any AE	117(49%)	118(50%)
Any drug-related AE	84(35%)	81(34%)
Any serious AE	10 (4%)	24 (10%)
Discontinuation due to AE	6(2%)	12(5%)

- Most adverse events were mild or moderate in intensity.
- The most common severe adverse events reported in the moxifloxacin treated patients included severe back pain (2 patients), severe insomnia (2 patients), and pneumonia (2 patients).
- The most common severe adverse events reported in the clarithromycin treated patients included severe headaches (5 patients), severe vomiting (4 patients), and severe nausea (3 patients).
- The most common adverse events reported in the moxifloxacin treated group included nausea (9%), diarrhea (8%), and headache (7%). The most common drug-related adverse events reported by moxifloxacin treated patients were GI-related: nausea (9%), diarrhea (8%), and vomiting (5%).
- The most common adverse events reported in the clarithromycin treated patients included diarrhea (12%), nausea (9%), and taste perversion (7%). The most common drug-related adverse events reported by clarithromycin treated patients included: diarrhea (9%), nausea (8%), and taste perversion (7%).

Citation: Hoeffken G, Meyer HP, Winter J, et al. The efficacy and safety of two oral moxifloxacin regimens compared to oral clarithromycin in the treatment of community-acquired pneumonia. *Respir Med.* 2001;95:553-564.

Location	Start Date and Duration	Trial Design	Inclusion Criteria
50 centers in 15 countries (Austria, Australia, Germany, Great Britain, Greece, Hong Kong, Israel, Indonesia, New Zealand, Norway, Philippines, South Africa, Sweden, Switzerland, and Taiwan)	November 26, 1996 to February 5, 1998 (1st patient's 1st visit to last patient's last visit)	Prospective, randomized, multi-national, multi-center, 3 armed, active-controlled, double-blind	• Outpatients of either sex who were at least 18 years with fever (core temp > 38.5°C or oral temp > 38°C) and/or leukocytosis • ≥ 1 of following: productive cough, purulent sputum, dyspnea or tachypnea, rigor/chills, pleuritic chest pain, and rales/rhonchi indicating consolidation • Radiological evidence of new or progressive infiltrate consistent w/pneumonia

Sample Characteristics – No. of Patients

	ITT	PP	Microb ITT	Microb PP
Rx1	229	180	52	40
Rx2	224	177	54	47
Rx3	222	174	52	41
Total	675	531	158	128

ITT = intent to treat
PP = per protocol.

Treatment and Dosage Regimens

- **Rx1:** Moxifloxacin 200 mg PO QD
- **Rx2:** Moxifloxacin 400 mg PO QD
- **Rx3:** Clarithromycin 500 mg PO b.i.d.

All three treatments given for 10 days with water before or with meal

Criteria for Evaluation

Efficacy

Primary – Clinical response at 3-5 days post-therapy (EOT)
Secondary – Clinical response 21-28 days post-therapy (follow-up), bacteriological response 3-5 days and 21-28 days post-therapy, clinical and bacteriological response 3-5 days post-start of therapy.

Safety

Clinical adverse reactions, blood and urine samples for hematology and biochemical analysis, and clinical variables

- In the PP and ITT populations, the 3 treatment groups were comparable on age, sex, weight and BMI, and concomitant medication. No significant differences with regards to baseline signs and symptoms of community-acquired pneumonia

Clinical Cure Rate at End of Therapy (PP Population)

	No. of Patients	Cures	Cure Rate
Rx1	180	169	93.9%
Rx2	177	167	94.4%
Rx3	174	164	94.3%

Bacteriological Success at End of Therapy (Microb PP Population)

	No. of Patients	Success	Success Rate
Rx1	40	29	72.5%
Rx2	47	37	78.7%
Rx3	41	29	70.7%

Clinical Cure Rate at Follow-Up (PP Population)

	No. of Patients	Cures	Cure Rate
Rx1	161	146	90.7%
Rx2	152	141	92.8%
Rx3	153	141	92.2%

Bacteriological Success at Follow-Up (Microb PP Population)

	No. of Patients	Success	Success Rate
Rx1	40	25	62.5%
Rx2	47	25	53.2%
Rx3	41	28	68.3%

Summary of Adverse Events (ITT Population)

	Rx1 (n=229)	**Rx2 (n=224)**	**Rx3 (n=222)**
Any AE	113 (49.3%)	114 (50.9%)	111 (50.0%)
Any drug-related AE	82 (35.8%)	84 (37.5%)	81 (36.5%)
Any serious AE	17 (7.4%)	22 (9.8%)	19 (8.6%)
Discontinuation due to AE	7 (3.1%)	2 (0.9%)	5 (2.3%)

- The majority of severe events were unrelated to the study medication. Severe events that were judged to be possibly or probably related to the study medication included pancreatitis (1) and gastrointestinal hemorrhage (1) in the moxifloxacin 200 mg group; deep thrombophlebitis (1) and sepsis and pneumonia (1) in the moxifloxacin 400 mg group; and respiratory acidosis (1) in the clarithromycin group.
- Of adverse events, percentage that were mild or moderate: 92.9% (195/210) in moxifloxacin 200-mg group, 93.0% (227/244) in moxifloxacin 400-mg group, and 89.7% (192/214) in clarithromycin 500-mg group
- Of adverse events, percentage that were resolved before end of study: 74.3% (156/210) in moxifloxacin 200-mg group, 74.2% (181/244) in moxifloxacin 400-mg group, and 77.1% (165/214) in clarithromycin 500-mg group
- Twelve patients died during the study: 5 patients in moxifloxacin 200-mg group, 2 patients in the moxifloxacin 400-mg group, and 5 patients in the 500-mg clarithromycin group.

Summary of Drug-Related Adverse Events by Symptoms Observed in at least 2% of Any Treatment Group

Adverse Events	**Rx1 (n=229)**	**Rx2 (n=224)**	**Rx3 (n=222)**
Diarrhea	13 (5.7%)	19 (8.5%)	8 (3.6%)
Liver function test abnormal	8 (3.5%)	16 (7.1%)	13 (5.9%)
Nausea	9 (3.9%)	9 (4.0%)	8 (3.6%)
Abdominal pain	9 (3.9%)	8 (3.6%)	3 (1.4%)
Oral moniliasis	6 (2.6%)	2 (0.9%)	2 (0.9%)
Headache	4 (1.7%)	7 (3.1%)	4 (1.8%)
Vomiting	3 (1.3%)	5 (2.2%)	4 (1.8%)
Nausea and vomiting	2 (0.9%)	5 (2.2%)	5 (2.3%)
Taste perversion	3 (1.3%)	2 (0.9%)	8 (3.6%)

- The most frequently reported drug-related adverse events were diarrhea in the moxifloxacin 200 mg and 400 mg treatment groups (5.7% and 8.5%, respectively) and liver function test abnormalities in the clarithromycin group (5.9%).

Citation: Katz E, et al. Safety and Efficacy of sequential (IV to PO) moxifloxacin vs conventional combination therapies, for the treatment of community-acquired pneumonia in patients requiring initial IV therapy. *J Emerg Med*. 2004;27:395-405.

Location	Trial Design	Inclusion Criteria
40 centers in United States	Trial run from March 2001 to April 2002. Multi-centered, prospective, randomized, parallel group open-label, Phase III study	• Adult subjects = 18 years of age who required initial IV therapy. • Patients included in the study presented with documented CAP or nursing home-acquired pneumonia and included cases of suspected aspiration or anaerobic pneumonia. • Radiologic evidence of a new or progressive pulmonary infiltrate consistent with pneumonia (based on radiologist's written report confirming the presence of a pneumonic infiltrate) and the presence of at least two characteristic signs or symptoms of pneumonia, including a productive cough with purulent or mucopurulent sputum, tracheobronchial secretions (> 25 polymorphonuclear cells [PMNs]/low-power field [LPF] on Gram stain), or change in the character of sputum (increased volume or purulence); dyspnea or tachypnea (respiratory rate >20 breaths/minute); rigors or chills; pleuritic chest pain; auscultatory findings on pulmonary examination of rales/crackles and/or evidence of pulmonary consolidation; fever (e.g., oral temperature > 38°C/100.4°F or hypothermia (rectal or core temperature < 35°C/95.2°F); and white blood cell (WBC) count = 10,000/µL or = 15% immature neutrophils (bands), regardless of the peripheral WBC count, or leukopenia with a total WBC count < 4500/µL.

Sample Characteristics – No. of Patients

	Moxifloxacin	Comparator	Total
ITT	167 (100%)	168 (100%)	335
PP	108 (64%)	113 (67%)	221
Valid for Microbiology	22 (13%)	28 (17%)	50

ITT = intent to treat (valid for safety)
PP = per protocol (valid for efficacy).

- In the comparator treated group (ITT population), 47 subjects received ceftriaxone alone, 111 received ceftriaxone plus azithromycin, 3 received ceftriaxone plus metronidazole, and 7 received ceftriaxone, azithromycin, and metronidazole.

Treatment and Dosage Regimens

Group 1: sequential IV/PO moxifloxacin 400 mg QD

Group 2: IV ceftriaxone 2 g QD followed by PO cefuroxime 500 mg b.i.d.

Group 2 subjects could also receive IV/PO azithromycin for suspected cases of atypical pneumonia (500 mg IV QD for 2 days followed by 500 mg IV/PO QD for a total of 7 to 10 days for hospitalized subjects or 500 mg IV/PO first dose followed by 250 mg PO QD for 4 days for non-hospitalized subjects) and/or IV/PO metronidazole 500 mg every 6 h for suspected cases of aspiration or anaerobic pneumonia.

Criteria for Evaluation

Efficacy

Primary – Clinical response at test-of-cure (TOC) visit (7-14 days post-therapy)
Secondary – Bacteriological response at TOC

Safety

All subjects receiving at least one dose of study drug were evaluated for drug safety (intent-to-treat population). Chest x–rays were obtained at baseline and at the test of cure visit and blood and urine samples were collected for routine hematology, chemistry, coagulation, and urinalysis.

- The majority of the patients enrolled in this trial were admitted to the hospital via the Emergency Room.
- The majority of patients enrolled (approximately 98%) presented with CAP.
- Similar demographic and baseline medical characteristics were found in the ITT population between treatment groups.
- The moxifloxacin treated group comprised of a significantly greater number of patients with a greater average number of years of cigarette smoking compared to the comparator (33.1 vs 28.3 years, respectively) (P=0.04).

Clinical Cure Rates

Population	Moxifloxacin No./n (%)*	Comparator No./n (%)*
Test of cure (7-14 days post-therapy)		
Safety population	93/111 (83.7%)†	93/116 (80.2%)
Clinically valid population	90/108 (83.3%)‡	90/113 (79.6%)
Microbiologically valid population	18/22 (81.8%)§	17/28 (60.7%)
Late follow-up (21-31 days post-therapy)		
Safety population	94/115 (81.7%)†	87/113 (77.0%)
Clinically valid population	81/101 (80.2%)‡	74/99 (74.7%)

*Indeterminate and missing responses were excluded.

† 95% CI = -6.7%, 14.4% at the test-of-cure visit; 95% CI = –7.5%, 1 4.2% at late follow-up.

‡ 95% CI = -6.9%, 13.6% at the test-of-cure visit; 95% CI = –7.2%, 16.3% at late follow-up.

§ 95% CI = -3.1%, 45.3% at the test-of-cure visit.

Eradication Rates of Common Respiratory Pathogens at TOC Visit

Organism	Moxifloxacin No./n (%)		Comparator No./n (%)	
All pathogens*	14/17	82.3%	15/24	62.5%
Streptococcus pneumoniae	6/7	86%	7/9	78%
Haemophilus influenzae	2/3	67%	2/4	50%

*Includes eradication and presumed eradication. (95% CI = -7.1% to 47.6%)

- The mean length of treatment in both treatment groups was 9 days.
- The mean duration of IV treatment in both treatment groups was 3 days, however, fewer moxifloxacin treated patients (8[7%]) received IV therapy for the entire study duration compared to the comparator group (15[13%]). There was no statistically significant difference in the mean duration between groups.

Summary of Adverse Events (ITT Population)

Adverse Events (AEs)	Moxifloxacin (n = 167)	Comparator (n = 168)
Treatment emergent AE	107	97
Any drug-related AE	30 (18.0%)	27 (16.1%)
Discontinuation due to AE	19 (11.4%)	6 (3.6%)
Death	10	7

- 80% of drug-related AEs were judged to be mild to moderate in severity.
- The majority of deaths in both treatment groups was judged to be secondary to progression of the patient's illness or underlying illness.

Incidence Rates of Drug-Related Adverse Events Occurring in = 2% of Patients

Adverse Event	Moxifloxacin (n = 167)	Comparator (n = 168)
Any drug-related event	30 (18.0%)	27 (16.1%)
Constipation	4 (2%)	1 (< 1%)
Nausea	3 (2%)	3 (2%)
Urticaria	3 (2%)	1 (< 1%)
Diarrhea	2 (1%)	10 (6%)
Headache	2 (1%)	4 (2%)
Vomiting	1 (< 1%)	3 (2%)

Citation: Lode H, Grossman C, Choudhri S, et al. Sequential IV/PO moxifloxacin treatment of patients with severe community-acquired pneumonia. *Respir Med*. 2003;97:1134-1142.

Location	Trial Design	Inclusion Criteria	Exclusion Criteria
Pooled data from 2 prospective randomized trials: one study conducted in Europe, Israel, and South Africa; the other study was conducted in North America	• One multi-national, open-label study, patients were randomized to either IV/PO moxifloxacin or IV/PO amoxicillin/ clavulanate ± IV/PO clarithromycin • One multi-center, prospective, double-blinded, phase III, North American study, patients were randomized to either IV/PO moxifloxacin QD or a comparator IV/PO fluoroquinolone (IV/PO alatrofloxacin/ trovafloxacin or IV/PO levofloxacin)	Inclusion criteria for both studies from which this retrospective analysis was conducted included: Patients = 18 years of age with mild to moderately severe CAP or severe CAP requiring IV therapy clinically documented by: • Presence of fever and/or elevated white blood cell count (>10,000/mm^3) • New or progressive infiltrate on a chest radiograph • Patient had to have at least one sign or symptom of pneumonia For this retrospective analysis study, only those patients identified as having severe CAP were included.	Patients were excluded for the following reasons: residing in a nursing home, hospitalization > 48 hours prior to pneumonia onset, bronchial obstruction or post-obstructive pneumonia or aspiration pneumonia or pulmonary tuberculosis, prior therapy with systemic antibiotic for > 24 hours prior to enrollment, moderate to severe liver or renal impairment, prolonged QTc interval, using Class IA or III antiarrhythmics, uncorrected hypokalemia, absolute neutrophil count <1000 cells/mm^3, or significant immunosuppression, and rapidly fatal underlying disease

Sample Characteristics – No. of Patients			
	Moxifloxacin	**Comparator**	**Total**
ITT	241	238	479
PP	190	186	376
MV	68	64	132

ITT = intent to treat
PP = per protocol (clinically valid)
MV = microbiologically valid.

Treatment and Dosage Regimens

Moxifloxacin – IV/PO 400 mg QD

Comparator – consisting of IV/PO amoxicillin/clavulanate (1200/625 mg t.i.d.) ± IV/PO clarithromycin (500 mg b.i.d.);
or
IV/PO alatrofloxacin/ trovafloxacin 200 mg QD (later changed to IV/PO levofloxacin 400 mg QD after concerns of hepatotoxicity)

In both arms, patients were treated for 7 - 14 days and received IV antibiotic (60-min infusion) for at least 3 days

Criteria for Evaluation

Efficacy

Clinical efficacy is reported for the test of cure visit for both trials:
- 5-7 days post-therapy in the multi-national trial
- 7-30 days post-therapy for the North American trial

Clinical assessment conducted to switch to the oral antibiotic included:
Resolution of fever, improved cough and respiratory distress, improvement in leukocytosis, chest radiographs, ability to tolerate oral therapy, no evidence of gastrointestinal motility or malabsorption, and the investigator's judgement.

Safety

All patients who received at least one dose of moxifloxacin were evaluated for safety. Safety was monitored by clinical observations and by conventional laboratory tests

- Demographic and baseline medical characteristics of the ITT and PP populations were similar between both treatment groups.
- Severe CAP was defined as per the 1993 ATS guidelines.

Clinical Resolution at Test of Cure in Patients with Severe CAP

Population	Moxifloxacin n/N (%)	Comparator n/N (%)
ITT Population[a]	171/241 (71%)	161/238 (68%)
PP Population[b]	167/190 (88%)	155/186 (83%)
MV Population[c]	59/68 (87%)	54/64 (84%)

[a]95% CI = –4.4%, 12%.
[b]95% CI = –1.9%, 12.2%.
[c]95% CI = –8.6%, 15%.

- A significantly greater number of moxifloxacin treated patients (73% [139/190]) switched from IV to PO therapy by day 5 of treatment compared to the comparator treated patients (60% [112/186]) (P<0.01).
- The mean length of antibiotic therapy was 12 ± 3 days for both treatment groups.

Summary of Adverse Events (ITT Population)

Adverse Events (AEs)	Moxifloxacin (n = 241)	Comparator (n = 238)
Any drug-related AE	116 (48%)	107 (45%)
Discontinuation due to AE	19 (8%)	13 (5.5%)

Incidence of Drug-Related Adverse Events Occurring in > 2% of patients				
Adverse Event	**Moxifloxacin (n = 241)**		**Comparator (n = 238)**	
Any drug-related event	116	(48%)	107	(45%)
Injection site reaction/phlebitis	12	(5%)	17	(7%)
Diarrhea	15	(6%)	14	(6%)
Nausea	8	(3%)	8	(3%)
Dizziness	5	(2%)	4	(2%)
Headache	5	(2%)	3	(1%)
Vomiting	5	(2%)	7	(3%)
Rash	3	(1%)	5	(2%)
LFT abnormalities	11	(5%)	12	(5%)
Oral moniliasis	5	(2%)	6	(3%)
Insomnia	5	(2%)	2	(<1%)
Atrial fibrillation	5	(2%)	0	(0%)
GGTP increased	1	(<1%)	5	(2%)

- Death was reported in 15 (6%) of moxifloxacin treated patients and 24 (10%) of comparator treated patients. In both treatment groups, the majority of deaths were judged to be related to progression of the patient's infection, development of nosocomial infection, or to underlying illness.

Citation: Torres A, Muir J-F, Corris P, et al. Effectiveness of oral moxifloxacin in standard first-line therapy in community-acquired pneumonia. *Eur Respir J*. 2003;21:135-143.

Location	Trial Design	Inclusion Criteria	Exclusion Criteria
64 participating centers in 13 countries	Phase IIIb, patients randomized to either moxifloxacin or to standard oral therapy for up to 14 days using a double-blind procedure, choice of stand. regimen made by investigator prior to random. based on clin. presentation	Patients = 18 years of age with CAP clinically documented by: • Presence of fever • Elevated white blood cell count (>100,000 μL^{-1}) • Signs or symptoms of pneumonia; • New or progressive infiltrate on a chest radiograph	Patients were excluded for the following reasons: allergy to fluoroquinolones, pregnancy or lactating, hospitalization for > 48 hours, rapid fatal underlying disease, history of fluoroquinolone tendinopathy, severe liver or renal impairment, administration of another investigational drug within 90 days of enrollment, previous enrollment in this study, drug treatment known to affect cardiac output interval, and previous systemic use of antibiotics for > 24 hours prior to enrollment

Sample Characteristics – No. of Patients

	Moxifloxacin	Standard*	Total
Randomized	278	285	563
ITT	233	244[†]	477
PP	215	231[‡]	446

ITT = intent to treat; PP = per protocol.
*Three different treatments in standard treatment arm: amoxicillin alone, clarithromycin alone, or amoxicillin + clarithromycin.
[†]In ITT comparator standard treatment arm: amoxicillin (41), clarithromycin (60), amoxicillin + clarithromycin (143).
[‡]In PP comparator standard treatment arm: amoxicillin (37), clarithromycin (57), amoxicillin + clarithromycin (137).

Treatment and Dosage Regimens

- **Moxifloxacin** PO 400 mg q.d.
- **Comparator** consisting of three standard PO treatments:
  - Amoxicillin 1 g t.i.d.
  - Clarithromycin 500 mg b.i.d.
  - Both amoxicillin and clarithromycin together

In both arms, patients received between 5-15 days of treatment

Criteria for Evaluation

Efficacy

- Patients were examined at:
  Primary -
  Days 7-10 of treatment (test-of-cure visit)

  Secondary -
  Days 3-5 of treatment
  Days 28-35 after the end of treatment
- **Clinical assessment** included:
  Physical examination, blood pressure, cardiac frequency, respiration rate and mental state (on entry only). Temp. recorded every 12 hours for first 5 days, bacteriological examination optional

Safety

All patients who received at least one dose of moxifloxacin were evaluated for adverse events Routine laboratory exams were conducted at baseline and then repeated as per the investigators discretion based on abnormal results or clinical judgement.

- Demographic characteristics, medical history, presenting sings and symptoms and the PSI were found to be similar between treatment groups.

Clinical Success Rates at Test of Cure (TOC) and Follow-Up (Per-Protocol [PP] and Intent-to-Treat [ITT] Populations)				
	TOC (7-10 Days)		Follow-Up (28-35 Days)	
	Moxifloxacin	Standard Treatment	Moxifloxacin	Standard Treatment
PP Population				
Success	201/215 (93.5%)	217/231 (93.9%)	183/192 (95.3%)	207/221 (93.7%)
95% confidence interval	(–4.2, 3.3)		(–2.2, 5.2)	
ITT Population				
Success	218/233 (93.6%)	229/244 (93.9%)	196/208 (94.2%)	218/234 (93.2%)
95% confidence interval	(–3.9, 3.3)		(–2.9, 4.8)	

- Oral moxifloxacin monotherapy was as effective as, and better tolerated than, optimal antibiotic strategy represented either by mono- or combination therapy (amoxicillin and/or clarithromycin) in community-acquired pneumonia management
- Results suggest, according to recent ATS guidelines, that quinolones for non-hospitalized CAP patients may be given at the same level of efficacy as ß-lactams and macrolides
- Moxifloxacin was significantly better tolerated than standard treatment with fewer drug-related adverse events

Summary of Adverse Events (ITT Population)

Adverse Events (AEs)	Moxifloxacin (n = 274)	Comparator (n = 279)
Overall incidence of any AE	132 (48%)	150 (54%)
AE possibly related to therapy	55 (20%)	86 (31%)*
Diarrhea	13 (4.7%)	22 (7.9%)
Nausea	10 (3.6%)	5 (1.8%)
Dizziness	1 (0.4%)	3 (1.1%)
Headache	5 (1.8%)	4 (1.4%)
Taste perversion	1 (0.4%)	6 (2.2%)
Serious or life - threatening AE	24 (9%)	33 (12%)
Premature Termination (AE)	25 (9%)	23 (8%)
Deaths	4	5

*p=0.004.

- The incidence of AEs judged to be related to the study drug in the moxifloxacin treated patients was statistically significantly lower than the comparator treated patients (20% vs 31%, respectively) (p=0.004).

Section 2.1.a.2
Pivotal Safety and Efficacy Trials -Acute Bacterial Sinusitis

Citation: Burke T, Villanueva C, Mariano H, et al. Comparison of moxifloxacin and cefuroxime axetil in the treatment of acute maxillary sinusitis. *Clin Ther*. 1999;21(10):1664-1677.

Location	Start Date and Duration	Trial Design	Inclusion Criteria ABMS = acute bacterial maxillary sinusitis
50 centers in the United States	February 16, 1998, to August 25, 1998 (1st patient's 1st visit to last patient's last visit)	Prospective, randomized, multi-center, double-blind, phase III	• Outpatient men and women 18 years or older • Documented or suspected ABMS (duration > 7 days but ≤ 28 days), evidenced by clinical signs and symptoms of acute infection and pos. x-ray (Water's view), • Two or more of the following symptoms: nasal congestion, postnasal discharge, purulent nasal drainage, frequent coughing or throat clearing, frontal headache, and malar tenderness or pain • Positive radiographic criteria including: air fluid level, opacification, or mucosal thickening > 6 mm • Females of childbearing age using reliable contraception during exposure to study drug

Sample Characteristics – No. of Patients			
	Moxifloxacin	**Comparator**	**Total**
Randomized	267	275	542
ITT	263	274	537
PP	223	234	457

ITT = intent to treat (valid for safety)
PP = per protocol (valid for efficacy.

Treatment and Dosage Regimens

- **Rx1:** Moxifloxacin 400-mg tablet QD PO 10 for days
- **Rx2:** Cefuroxime axetil 250 mg PO b.i.d. for 10 days

Criteria for Evaluation

Efficacy

- **Primary** – Clinical response at test-of-cure (TOC) 7-14 days post-treatment
- **Secondary** – Clinical response at follow-up 27-31 days post-treatment

Safety

On basis of physical exam findings, adverse events, electrocardiograms, intercurrent illness, and laboratory tests

- Treatment groups were similar with respect to demographics and baseline variables, *except* that moxifloxacin had fewer patients with moderate infections (74% vs 83%, $P = 0.033$), more patients with left sinus infection in last 6 months (6% moxifloxacin vs 2% cefuroxime axetil, $P = 0.050$), and more severe infections (21% moxifloxacin vs 15% cefuroxime axetil)

Clinical Success Rate

Response	Number (%) of Patients	
	Moxifloxacin	Cefuroxime axetil
7-21 days after therapy	**(n=223)**	**(n=234)**
Resolution*	200 (90)	209 (89)
Failure	23 (10)	25 (11)
27-31 days after therapy	**(n=184)**	**(n=202)**
Continued resolution	181 (98)	197 (98)
Relapse	3 (2)	5 (2)

* Resolution versus failure: 95% confidence interval, -5.1% to 6.2%.

- No significant difference in resolution rate between 2 treatment arms

Summary of Adverse Events (ITT Population)

Adverse Events (AE)	Moxifloxacin (n = 263)	Cefuroxime Axetil (n = 274)
Any adverse event	126 (48%)	112 (41%)
Any drug-related AE	96 (37%)	70 (26%)
Any serious AE	7 (3%)	10 (4%)
Discontinuation due to AE	15 (6%)	6 (2%)

- A greater proportion from moxifloxacin group withdrew from the study [10% as compared with 7% from cefuroxime axetil group), primarily due to a higher proportion of discontinuations due to adverse events 15 (6%) in moxifloxacin group vs 6 (2%) in cefuroxime axetil group]

Drug-Related Adverse Events Occurring in a Least 2% of Either Treatment Group (ITT Population)

Adverse Event	Moxifloxacin (n = 263)	Cefuroxime Axetil (n = 274)
Any body system	96 (37%)*	70 (26%)
Body as a whole	25 (10%)	15 (5%)
Nervousness	7 (3%)	2 (< 1%)
Asthenia	5 (2%)	4 (1%)
Central nervous system		
Dizziness	13 (5%)	7 (3%)
Headache	12 (5%)	8 (3%)
Gastrointestinal system		
Nausea	28 (11%)*	11 (4%)
Diarrhea	18 (7%)	17 (6%)
Vomiting	9 (3%)	3 (1%)
Abdominal Pain	5 (2%)	3 (1%)
Skin and appendages	9 (3%)	8 (3%)
Special senses	3 (1%)	9 (3%)
Urogenital	3 (1%)	8 (3%)

*p = 0.003 compared with cefuroxime axetil.

- More patients in moxifloxacin group reported events of moderate intensity than patients in cefuroxime axetil [62/126 (49%) vs 43/112 (38%) of all adverse events]
- Only 5% of patients in each treatment group reported events of severe intensity

Citation: Data on File. Schering-Plough Corporation. Kenilworth, New Jersey.

Location	Trial Design	Study methods
• The study was performed using data from the PharMetrics' database which contains demographic information and medical and pharmaceutical claims for more than 55 million patients that cover over 2 billion healthcare transactions, including prescriptions, office visits, hospital stays, and diagnostic tests from at least 75 different health plans. The database includes both inpatient and outpatient diagnoses and procedures, both retail pharmacy and mail order prescription records, as well as data on Medicare Risk patients.	A retrospective, claims database study conducted between April 2000 and March 2002.	Treatment episodes were selected from the database by first identifying all office or hospital outpatient visits with an ICD-9 diagnosis of acute sinusitis (AS). For each visit, the date of the diagnosis of acute sinusitis was determined to be the episode index date. The database was then searched for all episodes in which moxifloxacin or levofloxacin were prescribed within five days from the episode index date. The date of the prescription for either moxifloxacin or levofloxacin was defined as the drug index date. Inclusion and exclusion criteria were established *a priori* and applied to the treatment episodes that were used in the analyses to maximize the likelihood that the drug was being prescribed to treat acute sinusitis. The treatment episodes were monitored for a 30 day period following the drug index date, or in the case of treatment failure, for 30 days after the second antibiotic prescription was filled and continued until no treatment failure was observed.

Sample Characteristics – No. of Acute Sinusitis Episodes	Treatment	Criteria for Evaluation
Moxifloxacin 3,358 **Levofloxacin** 1,522 • The sample size above reflects the number of AS episodes in which the listed product was the initial treatment. • Baseline characteristics were similar between the two groups with the exception of a few differences which were significant. • Moxifloxacin treated patients had fewer patients with a compromised immune history (24.8% moxifloxacin, 28.7% levofloxacin, p = 0.003) and fewer episodes beginning in an emergency department (0.1% moxifloxacin, 0.5% levofloxacin, p = 0.008). • Log-lagged charges (the sum of the charges from all facility, professional service, and outpatient claims that occurred in the 180-day period prior to the beginning of the treatment episode) were lower in the moxifloxacin group at baseline (6.17 moxifloxacin, 6.39 levofloxacin, p = 0.008).	AS episodes were included in the study analysis, only where either moxifloxacin or levofloxacin were identified as the initial therapy.	• Endpoints measured in this study included total therapy duration and monotherapy duration, treatment failure, recurrence of infection, and treatment costs.

Results

Ordinary Least Squares Regression Results*

	Duration of original prescription (days supplied)	Monotherapy duration (days supplied)	Duration of all antibiotics (days supplied)	Treatment Charges ($)	Log of treatment charges ($)
Treatment (moxifloxacin=1) *Estimate (p-value)*	-1.65 *(<0.0001)*	-2.06 *(<0.0001)*	-1.97 *(<0.0001)*	-37.94 *(<0.0001)*	-0.093 *(<0.0001)*
F statistic	26.59 *(<0.0001)*	26.75 *(<0.0001)*	22.67 *(<0.0001)*	5.12 *(<0.0001)*	23.26 *(<0.0001)*
R^2	0.047	0.049	0.040	0.009	0.041

* All regression models controlled for: diabetes, compromised immune history, log lagged charges, start of episode in the emergency department, acute steroid use, gender, Charlson-Deyo comorbidity score, and age.

- The average duration of therapy was 10.4 days in the moxifloxacin group versus 12.4 days in the levofloxacin group ($p < 0.001$).
- Moxifloxacin treated patients had a 36% lower probability of recurrence than levofloxacin treated patients ($p=0.0062$).
- The observed failure rate was also significantly lower in the moxifloxacin group compared to the levofloxacin group (10.4% versus 14%, respectively, $p = 0.003$).
- Cost analysis also demonstrated that the average total treatment charges ($171 moxifloxacin verses $211 levofloxacin, $p = 0.03$) and average pharmacy charges ($103 moxifloxacin versus $117 levofloxacin, $p < 0.0001$) were significantly lower in the moxifloxacin-initiated group (costs were adjusted to 2002 dollars using the Consumer Price Index).
- Ordinary least squares analysis demonstrated that the duration of the original prescription was 1.65 days shorter for the moxifloxacin group compared to the levofloxacin group.
- The duration of therapy, both monotherapy and duration of all antibiotics, was significantly shorter in the moxifloxacin treated group when compared to the levofloxacin group (2.06 and 1.97 days, respectively, $p<0.0001$).

Citation: Baz MN, Jannetti W, Villaneuva C et al. The efficacy and tolerability of moxifloxacin compared to trovafloxacin in the treatment of acute sinusitis. *Today's Ther Trends*. 1999;17:303-319.

Location	Trial Design	Inclusion Criteria
46 centers in the United States	Prospective, multi-center, randomized, double-blind	• Outpatient men and women at least 18 years of age • Diagnosis of acute bacterial sinusitis defined as presence of clinical signs and symptoms = 7 days but = 28 days in duration with radiologic paranasal x-ray confirming maxillary sinusitis • At least 2 of the following: nasal congestion, post-nasal discharge, frequent coughing or throat clearing, frontal headache, malar tenderness/pain

Sample Characteristics – No. of Patients				Treatment and Dosage Regimens	Criteria for Evaluation
	Moxifloxacin	Trovafloxacin	Total	**Moxifloxacin** 400 mg tablet QD for 10 days, placebo for evening doses days 1-7, and both doses days 8-10 **Trovafloxacin** 200 mg tablet QD for 10 days	***Efficacy*** **Primary** - Clinical response and follow-up sinus x-ray at test-of-cure visit (7-21 days post-treatment) ***Safety*** Clinical adverse events, blood chemistry, hematology, and urinalysis
ITT	288	302	590		
PP	253	260	513		
ITT = intent to treat (valid for safety) PP = per protocol (valid for efficacy)					

Clinical Response

Time of Evaluation	Response	Moxi n (%)	Trov n (%)	95% CI
PP 7-21 days post-therapy*	Resolution	223 (88.1%)	232 (89.2%)	-6.5%, 3.9%
	Failure	29 (11.5%)	27 (10.4%)	
	Response	1 (0.4%)	1 (0.4%)	
ITT 7-21 days post-therapy	Resolution	238 (82.6%)	244 (80.8%)	-6.0%, 4.2%
	Failure	31 (10.8%)	29 (9.6%)	
	Response	1 (0.3%)	1 (0.3%)	

*Primary endpoint

- Moxifloxacin treatment was found to be statistically equivalent to trovafloxacin
- Trovafloxacin patients reported a statistically and clinically significant 4-fold greater incidence of dizziness (19%) than moxifloxacin recipients (5%, $P < 0.001$)
- A significantly higher proportion of moxifloxacin-treated patients completed the full treatment regimen

Incidence of Drug-Related Events Occurring in = 2% of Patients

Adverse Event	Moxi (n=288)	Trov (1=302)
Any Event	96 (33%)	113 (37%)
Headache	9 (3%)	21 (7%)
Nausea	34 (12%)	28 (9%)
Diarrhea	19 (7%)	9 (3%)
Vomiting	5 (2%)	12 (4%)
Abdominal pain	5 (2%)	2 (<1%)
Dizziness	13 (5%)	56 (19%)
Nervousness	5 (2%)	4 (1%)
Paresthesia	0 (0%)	5 (2%)
Taste perversion	5 (2%)	1 (<1%)
Vaginal moniliasis	5 (2%)	2 (<1%)

Citation: Siegert R, Gehanno P, Nikolaidis P, et al. A comparison of the safety and efficacy of moxifloxacin (BAY 12-8039) and cefuroxime axetil in the treatment of acute bacterial sinusitis in adults. *Respir Med*. 2000;94:337-344.

Location	Start Date and Duration	Trial Design	Inclusion Criteria
60 centers in 7 countries	November 21, 1996, to June 25, 1997 (1st patient's 1st visit to last patient's last visit)	Prospective, 2 armed, randomized, multi-center, double-blind, parallel-group, active-controlled	• Outpatient men and women at least 18 years of age • Suffering from acute bacterial sinusitis either bacteriologically documented or clinically suspected using radiological paranasal sinus x-ray • At least 2 of the following: nasal congestion, post-nasal drainage, frequent coughing or throat clearing, frontal headache, malar tenderness/pain, purulent nasal drainage

Sample Characteristics – No. of Patients				Treatment and Dosage Regimens	Criteria for Evaluation
	Moxifloxacin	**Cefuroxime**	**Total**	• **Rx1:** moxifloxacin 400 mg PO QD for 7 days, placebo for evening doses days 1-7, and both doses days 8-10 • **Rx2:** cefuroxime axetil 250 mg PO b.i.d. for 10 days	***Efficacy*** • **Primary** – Clinical response at end-of-therapy (EOT), defined as day 14 assessment, i.e., 3 days post-end of therapy • **Secondary** – Clinical response during therapy (days 7-9) and follow-up (days 27-31 after treatment) • **Secondary** – Bacteriological response at EOT (day 14)
Randomized	242	251	493		***Safety*** Clinical adverse events, blood chemistry, hematology, and urinalysis
ITT	242	251	493		
PP	211	225	436		
Microbiologically valid	109	115	224		
ITT = intent to treat (valid for safety) PP = per protocol.					

Clinical Response

Clinical Response at Day 14	Moxifloxacin	Cefuroxime Axetil	95% Confidence Interval
PP Population	**n = 211**	**n = 225**	1.5%; 10.6%
Resolution	204 (96.7%)	204 (90.7%)	
Failure	7 (3.3%)	21 (9.3%)	
ITT Population	**n=242**	**n=251**	-3.7%;7.8%
Resolution	216 (89.3%)	219 (87.3%)	
Failure	11 (4.6%)	22 (8.8%)	
Indeterminate	9 (3.7%)	7 (2.8%)	
Missing	6 (2.5%)	3 (1.2%)	

- Resolution rates in the PP population at Day 14 show that moxifloxacin is clinically more effective than Cefuroxime Axetil.
- Clinical success at the follow up (21-28 days after the end of therapy) showed that 90.7% moxi and 89.2% cef treated patients were assessed as successful (95% CI, -4.3%; 5.4%).
- In ITT population overall resolution rate at EOT was 89.3% in moxifloxacin and 87.3% in cefuroxime axetil
- At follow-up and combined EOT/follow-up, rate of continued resolution showed equivalence between treatment groups

Bacteriological Response at EOT (PP Population)

Bacteriological Response	Moxifloxacin (n=109)	Cefuroxime Axetil (n=115)
Bacteriological success rate	103 (94.5%)	96 (83.5%)
Eradication	41 (37.6%)	33 (28.7%)
Presumed eradication	62 (56.9%)	63 (54.8%)
Bacteriological failure rate	6 (5.5%)	19 (16.5%)
Eradication with superinfection	2 (1.8%)	7 (6.1%)
Persistence (includes persistence with superinfection)	2 (1.8%)	7 (6.1%)
Presumed persistence	2 (1.8%)	5 (4.3%)

- If eradication and presumed eradication were considered success and eradication with superinfection counted as bact. failure, the eradication rate was 94.5% (103/109) in moxifloxacin group and 83.5% (96/115) in cefuroxime axetil group
- 95% confidence interval for difference in bacteriological success rates by patients at EOT indicates superiority of moxifloxacin over cefuroxime axetil, but does not supply statistical proof because bacteriological response was a secondary efficacy variable
- Overall bacteriological success rate in ITT population at EOT similar in both groups; 84.4% in moxifloxacin group and 78.3% in cefuroxime axetil group

Summary of Adverse Events: Overview (ITT Population)

	Moxifloxacin (n=242)	Cefuroxime Axetil (n=251)
Any adverse event (AE)	105 (43.4%)	88 (35.1%)
Any drug-related AE	74 (30.6%)	56 (22.3%)
Any serious AE	3 (1.2%)	8 (3.2%)
Discontinuation due to AE	14 (5.8%)	11 (4.4%)

Summary of Adverse Events by Symptoms, Causal Relationship to the Study Drugs at Least Remote (ITT Population)

	Moxifloxacin (n=242)	Cefuroxime Axetil (n=251)
Diarrhea	23 (9.5%)	15 (6.0%)
Abdominal pain	10 (4.1%)	7 (2.8%)
Nausea	9 (3.7%)	5 (2.0%)
Vomiting	8 (3.3%)	4 (1.6%)
Vertigo	7 (2.9%)	2 (0.8%)

Citation: Gehanno P, Berche P, Perrin A. Moxifloxacin in the treatment of acute maxillary sinusitis after first-line treatment failure and acute sinusitis with high risk of complications. *J Int Med Res.* 2003;31:435-448.

Location	Trial Design	Inclusion Criteria
52 community ear, nose and throat practitioners throughout France	Prospective, multi-center study after first-line treatment failure (group 1), and acute sinusitis with high risk of complications (group 2)	• Eligible patients were men and women = 18 years of age, with suspected acute bacterial sinusitis and evidence of purulent rhinorrhoea confirmed by nasal endoscopy • Symptoms included nasal congestion and at least one of the following: spontaneous/induced infra-orbital pain, frontal cephalalgia, cough or frequent throat clearing, and temperature ≥ 38.0°C • Radiological and/or tomodensitometric tests were conducted within 48 hours prior to treatment initiation and were evaluated by the study coordinator (centralized review) • Acute sinusitis was confirmed if radiographs showed mucosal thickening of ≥ 6 mm and/or sinus opacity, and/or intra-sinus fluid. **Exclusion Criteria** • Suspected bacteremia or meningitis; history of sinus surgery; chronic sinusitis; > 2 episodes of sinusitis within the past 6 months; immunosuppression (neutropenia, documented HIV infection); need for concomitant systemic antimicrobial therapy; pregnancy or breast-feeding; documented hypersensitivity to moxifloxacin, its excipients, or other quinolones; renal impairment (baseline serum creatinine > 265 µmol/L); severe hepatic impairment or increased transaminase rate (×5 the upper limit of normal); congenital or acquired prolonged QT intervals; hydroelectrolytic disorders; uncorrected hypokalemia; clinically significant bradycardia, especially cardiac insufficiency through reduction of the left ventricular ejection fraction; previous history of clinically significant arrhythmia; and/or co-administration of other medications reported to prolong QT intervals.

Sample Characteristics – No. of Patients		Treatment and Dosage Regimens	Criteria for Evaluation
			Efficacy
Number of Patients		**Moxifloxacin** all patients were treated with 400 mg PO QD for 7 days	**Primary** - Clinical responses recorded on days 7-10 post-treatment (V3) **Secondary** - Clinical responses recorded on days 3-4 of treatment (V2)
Total	258		***Safety***
ITT Population	255		Safety monitored by clinical observations and lab tests of renal, hepatic, and hematological function. Adverse events subjectively rated by investigator as to severity and the relationship to study
PP Population	216		

ITT = intent to treat (valid for safety)
PP = per protocol (valid for efficacy).

- Group 1 (maxillary sinus after first-line treatment failure), n = 175; group 2 (sinusitis with risk of complications), n = 41
- 39 patients were excluded from the PP analysis for the following reasons: violation of inclusion/exclusion criteria, most frequently due to radiographs not supporting the diagnosis (18 patients); schedule violations of V3 (14 patients); and lack of clinical evaluation or an "indeterminate" evaluation at V3 (7 patients)
- The PP population comprised 216 patients (83.7%), 41 of whom had sinusitis with high risk of complications and 175 who had maxillary sinusitis after first-line treatment failure

Main Bacterial Species Isolated from Sinus Secretions from 92 of the 216 Patients in the Per Protocol Population at Inclusion, According to Sinusitis Type

Organisms	Maxillary Sinusitis After First-Line Treatment Failure	Sinusitis with Risk of Complications	Total (%)
S. pneumoniae	23	7	30 (29.4)
PSAP/PRSP	15	3	
H. influenzae	19	8	27 (26.5)
ß-lactamase producer	11	2	
Enterobacteriaceae	16	2	18 (17.6)
M. catarrhalis	11	1	12 (11.8)
S. aureus	8	2	10 (9.8)
Other Gram-negative bacilli	2	3	5 (4.9)
TOTAL	79	23	102 (100.0)

PSAP, pneumococcus with reduced susceptibility to penicillin G (0.1 mg/L < MIC < 1 mg/L).
PRSP, pneumococcus resistant to penicillin G (MIC > 1 mg/L).

Clinical Responses Observed During Treatment with Moxifloxacin, Post-Treatment and at Post-Treatment Follow-Up in All Patients Included in this Study of Sinusitis

	Intent-to-Treat Population (%)	Per Protocol Population (%)
Days 3-4 (V2)	(n = 255)	(n = 216)
Improvement	238 (93.3)	205 (94.9)
Failure	6 (2.4)	6 (2.8)
Indeterminate response/missing data	11 (4.3)	5 (2.3)
7-10 days post-treatment (V3)γ	(n = 255)	(n = 216)
Clinical success or completion resolution of all clinical signs and symptoms	230 (90.2)	200 (92.6)
Failure*	18 (7.1)	16 (7.4)
Indeterminate response/missing data	7 (2.7)	–
4-5 weeks post-treatment†	(n = 230)	(n = 200)
Continued resolution	226 (98.3)	198 (99.0)
Relapse	3 (1.3)	2 (1.0)
Missing data	1 (0.4)	–

γPrimary endpoint
*Failures occurring during treatment are included in visit V3.
†In patients considered resolved at V3.

Incidence of the Main Adverse Events* Possibly or Probably Related to Treatment of Sinusitis with Moxifloxacin in the ITT Population (n = 255)

Adverse Event (COSTART System)	Incidence, No. (%)†
Body as a whole	31 (12.2)
General	12 (4.7)
Abdominal pain	6 (2.4)
Asthenia	2 (0.8)
Cardiovascular system	3 (1.2)
Tachycardia	2 (0.8)
Gastrointestinal system	9 (3.5)
Nausea	6 (2.4)
Diarrhea	3 (1.2)
Musculoskeletal system	3 (1.2)
Arthralgia	2 (0.8)
Central nervous system	6 (2.4)
Dizziness	2 (0.8)
Tremor	2 (0.8)
Respiratory	1 (0.4)
Skin and mucous membranes	3 (1.2)
Rash	2 (0.8)
Neurosensorial	4 (1.6)
Visual abnormalities	2 (0.8)

*Only events that occurred = 2 times are reported.

†Incidence, ratio of the number of patients with adverse events to the number of patients valid for safety analysis.

Summary of Results

- The clinical success rate 7-10 days posttreatment was 92.6%. Bacteriological success rates were 95.7% after 3-4 days of treatment, and 97.2% and 95.2%, in group 1 and group 2, respectively, at 7-10 days post-treatment
- Drug-related adverse events, including abdominal pain (2.4%), nausea (2.4%), and diarrhea (1.2%), were reported in 12.2% of patients
- Overall, moxifloxacin therapy resulted in rapid bacteriological eradication, with a high rate of clinical success

Citation: Rakkar S, Roberts K, Towe BF, Flores SM, Heyd A, Warner J. Moxifloxacin versus amoxycillin clavulanate in the treatment of acute maxillary sinusitis: a primary care experience. *Int J Clin Pract*. 2001;55(5):309-315.

Location	Trial Design	Inclusion Criteria
85 primary care sites throughout the United States	Prospective, multi-center, randomized, non-blinded, phase III 2-arm, comparative study	• Outpatient men and non-pregnant women ≥ 18 years • Clinical diagnosis of acute suspected bacterial sinusitis (i.e., ≥ 7 days but <30 days duration) • Clinical signs and symptoms of sinusitis (e.g., nasal congestion, post-nasal drainage, frequent coughing or throat clearing, frontal headache, malar tenderness/pain, and purulent nasal discharge)

Sample Characteristics – No. of Patients

	Moxifloxacin	Amox/Clav	Total
Randomized	238	237	475
ITT	234	237	471
PP	170	171	341

ITT = intent to treat (valid for safety)
PP = per protocol (valid for efficacy).

- Patient population primarily consisted of Caucasian females under 45 years of age
- Reasons for exclusion of 134 from PP population were similar between the 2 treatment groups

Treatment and Dosage Regimens

- **Rx1:** moxifloxacin 400 mg QD PO for 10 days
- **Rx2:** amoxicillin clavulanate (amox/clav) 875 mg b.i.d. PO for 10 days

Criteria for Evaluation

Efficacy

- **Primary** – Clinical resolution at the test-of-cure (TOC) visit (14-21 days post-treatment)
- **Secondary** – Clinical relapse at follow-up (days 26-46 post-therapy visit)

Safety

Safety monitored by clinical observations and lab tests of renal, hepatic, and hematological function. Adverse events subjectively rated by investigator as to severity and the relationship to study

Clinical Efficacy

	ITT n (%)		PP n (%)	
Time of Evaluation	**Moxi**	**Amox/Clav**	**Moxi**	**Amox/Clav**
TOC (14-21 days post-therapy)				
Clinical Resolution	(85%)	(82%)	(86%)	(84%)
Follow-Up (26-46 days post-therapy)				
Clinical Recurrence	6	7	6 (4%)	6 (4%)

- The relationship between clinical response and certain baseline medical characteristics were investigated and a trend was identified in clinical response and duration of infection prior to initiating treatment. Patients whose duration of infection was =10 days before initiation study drug (93% moxi, 85% amox/clav) compared to those having an infection of >10 days duration (77% moxi, 82% amox/clav).

Drug-Related Adverse Events Reported in > 2% of Patients

Body System	Moxi (n=234)	Amox/clav (n=237)
	n (%)	n (%)
Any body system	71 (30)	60 (25)
Body as a whole	18 (8)	20 (8)
Moniliasis	5 (2)	7 (3)
Headache	3 (1)	5 (2)
Abdominal pain	5 (2)	2 (<1)
Asthenia	3 (1)	5 (2)
Digestive	44 (19)	34 (14)
Nausea	26 (11)	11 (5)
Diarrhea	7 (3)	24 (10)
Vomiting	7 (3)	2 (<1)
Nervous	9 (4)	5 (2)
Dizziness	6 (3)	0 (0)
Skin and appendages	5 (2)	4 (2)
Rash	4 (2)	2 (<1)
Special senses	7 (3)	3 (1)
Urogenital	4 (2)	9 (4)
Vaginal moniliasis	3 (1)	8 (3)

Patient-Reported Outcomes		
	Moxifloxacin	**Amox/Clav**
Mean No. of days until positive subjective response (ITT pop.)	6.8	6.9
By day 2 of Tx, patients reporting substantial symptom improvement	14	6
By day 3 of Tx, patients reporting feeling better	24% (47) (significant, $p < 0.02$)	14% (28)
Patients resuming normal activity within 3 days of therapy	38%	35%
Mean number of hours missed from work	7.1 hours	7.9 hours

Tx = therapy.

Overall, it appeared that moxifloxacin provided more rapid relief from sinus-related symptoms than the comparator agent

Citation: Gehanno P, Darantiere S, Dubreuil C, et al. A prospective, multi-centre study of moxifloxacin concentrations in the sinus mucosa tissue of patients undergoing elective surgery of the sinus. *J Antimicrob Chemother*. 2002;49:821-826.

Location	Trial Design	Exclusion Criteria
7 French hospitals	Multi-center, controlled, open-label, 7 non-parallel groups, and one control group	• Outpatient men and women = 18 years of age • Hypersensitivity to quinolones; pregnancy and lactation; recent participation in another clinical trial; liver enzyme abnormalities; raised creatinine; positive test for HIV, hepatitis C or B; any laboratory test result that could contraindicate sinus surgery

Sample Characteristics – No. of Patients	Treatment and Dosage Regimens	Blood and Tissue Samples
Valid for safety (PP) 48 PP = per protocol: 42 – moxifloxacin group; 6 – control group.	**Moxifloxacin** 400-mg tablet QD for 5 days **Group A** - last drug intake 2 h before surgery **Group B** - 3 h before surgery **Group C** - 4 h before surgery **Group D** - 6 h before surgery **Group E** - 12 h before surgery **Group F** - 24 h before surgery **Group G** - 36 h before surgery	• 2 specimens (1 blood sample and 1 tissue sample) were collected from each treated patient during the surgical procedure • Blood samples were drawn by venipuncture **Criteria for Evaluation** ***Efficacy*** • **Primary** - Concentration of moxifloxacin in sinus tissues and in plasma at sampling time ***Safety*** • **Secondary** - Clinical adverse events

Results

- The geometric mean moxifloxacin plasma concentration increased from 2.32 mg/L at 2 h to a maximum of 3.37 mg/L at 4 h post-dose, decreasing to 0.37 mg/L at 36 h post-dose
- The moxifloxacin concentration in sinus mucosa was consistently greater than that in plasma, being 4.56-5.73 mg/kg from 2 to 6 h and 2.81-1.25 mg/kg from 12 to 36 h post-dose. The elimination rates in plasma and sinus tissues were similar. The tissue/plasma ratio was ≈ 200% between 2 and 6 h, and up to 328.9% at 36 h
- Tissue levels exceeded the MIC_{90} of all pathogens commonly causing acute sinusitis (e.g., 5-30 × MIC for *Streptococcus pneumoniae*: 0.25 mg/L)

Section 2.1.a.3
Pivotal Safety and Efficacy Trials - Acute Exacerbations of Chronic Bronchitis

Citation: Chodosh S, DeAbate CA, Haverstock D, et al. Short-course moxifloxacin therapy for treatment of acute bacterial exacerbations of chronic bronchitis. *Respir Med.* 2000;94:18-27.

Location	Start Date and Duration	Trial Design	Inclusion Criteria
56 centers in United States	November 21 1996, to April 7 1998 (1st patient's 1st visit to last patient's last visit)	Prospective, randomized, double-blind, parallel	• Men or women 18 years or older • With acute bacterial exacerbations of chronic bronchitis • Increased purulent/mucopurulent sputum and at least 1 of following: increased cough, dyspnea, or sputum volume or the presence of fever (oral temperature > 100.4°F) at time of screening

Sample Characteristics – No. of Patients					Treatment and Dosage Regimens	Criteria for Evaluation
	Rx1	**Rx2**	**Rx3**	**Total**	• **Rx1:** moxifloxacin 400 mg PO QD x 5 days • **Rx2:** moxifloxacin 400 mg PO QD x 10 days • **Rx3:** clarithromycin 500 mg PO b.i.d. x 10 days Rx1 and Rx2 included placebo for uniform dosing	***Efficacy*** • **Primary** – Clinical response and bacteriological response at end of therapy (post-therapy days 0-6) and at follow-up (post-therapy days 7-17) ***Safety*** Physical exam findings, ECGs, adverse events, intercurrent illness, and lab tests
Randomized	316	307	313	936		
ITT	312	302	312	926		
PP	143	148	129	420		
ITT = intent to treat (valid for safety); P P = per protocol (valid for efficacy). • The 3 treatment groups were well matched demographically on age, sex, race distribution, smoking history, No. of acute bacterial exacerbations of chronic bronchitis (ABECB) events in last 12 months, and type of infection						

Clinical and Bacteriological Success Rates

	Rx1 No./n (%)	Rx2 No./n (%)	Rx3 No./n (%)
PP patients			
Clinical success			
EOT	127/135 (94)	136/144 (94)	121/127 (95)
Follow-up	127/135 (94)	134/140 (96)	118/123 (96)
Overall*	127/143 (89)	134/148 (91)	118/129 (91)
Bact. success			
EOT	127/135 (94)	138/145 (95)	115/127 (91)
Follow-up	127/143 (89)	135/148 (91)	110/129 (85)
ITT patients			
Clinical success			
EOT	274/288 (95)	266/281 (95)	268/286 (94)
Follow-up	242/256 (94)	250/258 (97)	232/245 (95)
Overall*	242/270 (90)	250/273 (92)	232/263 (88)
Bact. success			
EOT	142/152 (93)	156/165 (95)	130/144 (90)
Follow-up	130/149 (87)	144/159 (91)	113/136 (83)

EOT = end of therapy, 0-6 days post-therapy; follow-up = 7-17 days post therapy.

*Includes failures occurring by end of therapy that are carried forward in addition to clinical evaluation at follow-up.

Summary of Adverse Events

Adverse Events (AEs)	Rx1 (n = 312)	Rx2 (n = 302)	Rx3 (n = 312)
Any AE	42%	46%	48%
Any serious AE	7%	6%	10%
Patients w/at least 1 life-threatening AE	13	15	18
Discontinuation due to AE	4	4	7

Summary of Drug-Related Adverse Events by Symptoms Observed in at Least 2% of Either Treatment Group

Adverse Event	Rx1 (n = 312) No. (%)	Rx2 (n = 302) No. (%)	Rx3 (n = 312) No. (%)
Nausea	12 (4)	23 (8)	23 (7)
Diarrhea	15 (5)	18 (6)	15 (5)
Dizziness	9 (3)	14 (5)	4 (1)
Headache	7 (2)	7 (2)	2 (< 1)
Taste perversion	6 (2)	6 (2)	26 (8)
Vomiting	3 (< 1)	8 (3)	9 (3)
Dyspepsia	7 (2)	2 (< 1)	2 (< 1)
Asthenia	2 (< 1)	5 (2)	3 (< 1)
Nervousness	2 (< 1)	4 (1)	5 (2)
Flatulence	4 (1)	2 (< 1)	5 (2)
Pruritus	3 (< 1)	2 (< 1)	5 (2)

- Two patients died during the trial, one each in Rx1 and Rx3 groups. Neither occurred while patient was on study drug. Patient in Rx1 died of pancreatitis on day 36, while patient in Rx3 died from a presumed myocardial infarction on day 12

Citation: Hautamaki D, Bruya T, Kureishi A, Warner J, Church D. Short-course (5-day) moxifloxacin versus 7-day levofloxacin therapy for treatment of acute exacerbations of chronic bronchitis. *Today's Ther Trends*. 2001;19:117-136.

Location	Trial Design	Inclusion Criteria
42 centers across the United States	Prospective, randomized, double-blind	• Men and women 18 years or older with underlying chronic bronchitis defined by daily production of sputum on most days for ≥ 3 consecutive months for > 2 consecutive years and an ABECB of < 30 days duration • Must have had increased purulent/mucopurulent sputum (e.g., opaque, yellow-green, viscous material) and at least 1 of the following: increased cough, increased dyspnea, increased sputum volume, or presence of fever (oral temp > 38°C)

Sample Characteristics – No. of Patients				Treatment and Dosage Regimens	Criteria for Evaluation
	Moxiflox-acin	**Levoflox-acin**	**Total**	• **Moxifloxacin** 400 mg QD x 5 days (short course) • **Levofloxacin** 500 mg QD x 7 days	***Efficacy*** • **Primary** – Clinical response at test of cure (7-21 days) and follow-up (27-38 days) • **Secondary** – Bacteriological response at post-therapy (7-21 days) and follow-up (27-38 days) ***Safety*** Physical examination, adverse event, intercurrent illness and laboratory tests (hematology, blood chemistry and urinalysis tests)
Randomized	299	299	598		
ITT	296(99.0%)	298(99.7%)	594		
Clin. Valid	227(75.9%)	234(78.3%)	461		
Microb. Valid	131(43.8%)	129(43.1%)	260		

ITT = intent to treat.
- Clinical assessment and bacteriological evaluation performed pre-therapy, during the therapy (days 3-5), at the test-of-cure visit (post-therapy days 7 to 21), and at follow-up visit (post-therapy days 27 to 38)

- The treatment groups were well matched on age, gender, race distribution., smoking history and infection type.

Clinical Response Rate

	Moxifloxacin (n = 227)		Levofloxacin (n = 234)	
	Clin. Valid	ITT	Clin. Valid	ITT
Test of cure	93%	92%	94%	95%
Follow-up	89%	87%	90%	89%

- Baseline demographic characteristics did not appear to influence rates of clinical resolution between the treatment groups

Bacteriologic Response Rate
(Microb. Valid Population)

	Moxifloxacin	Levofloxacin
Eradication rates (incl. eradication and presumed eradication) at test of cure	126/131 (96%)	124/129 (96%)
Eradication rates at follow-up (excl. indeterminate responses)	87%	87%

- There were 13 superinfections (6 moxifloxacin, 7 levofloxacin) with no pathogen predominating
- Reinfections or recurrences were reported for 8 patients in each group
- Both treatment regimens were effective in eradicating 100% *of S. pneumoniae* isolates and > 96% of *H. influenzae* isolates

Adverse Events (AEs)	**Moxifloxacin**	**Levofloxacin**
Treatment emergent (AE)	114/296 (39%)	124/298 (42%)
Serious or life-threatening AE	11/296 (3.7%)	7/298 (2.3%)
Discontinuation due to AE	5/296 (1.7%)	4/298 (1.3%)

Drug-Related Adverse Events Occurring in at least 2% of Patients

Adverse Event	**Moxifloxacin- (n = 296)**	**Levofloxacin- (n = 298)**
Any drug-related event	72 (24%)	74 (25%)
Abdominal pain	7 (2%)	5 (2%)
Nausea	22 (7%)	15 (5%)
Diarrhea	15 (5%)	18 (6%)
Dry mouth	5 (2%)	7 (2%)
Dyspepsia	4 (1%)	7 (2%)
Vomiting	5 (2%)	1 (< 1%)
Constipation	0 (0%)	5 (2%)
Dizziness	11 (4%)	6 (2%)

- Only one cardiovascular event, a case of palpitation in the levofloxacin group, was considered to probably be drug related

Citation: Kreis SR, Herrera N, Golzar N, et al. A comparison of moxifloxacin and azithromycin in the treatment of acute exacerbation of chronic bronchitis. *J Clin Outcomes Manage*. 2000;7(12):33-37.

Location	Start Date and Duration	Trial Design	Inclusion Criteria
74 primary care practice sites across the United States	September 1999 to May 2000	Prospective, multi-center, non-blinded, phase IIIb	• Male or non-pregnant female outpatients 18 years or older with clinically documented ABECB of suspected bacterial origin and without a recent chest x-ray suggestive of a new pneumonia or lobar consolidation • Underlying chronic bronchitis defined by daily production of sputum on most days for ≥ 3 consecutive months for > 2 consecutive years • Symptoms of increased sputum purulence and at least 1 of the following: increased sputum volume, increased cough, or increased dyspnea or fever (> 38°C orally)

Sample Characteristics – No. of Patients				Treatment and Dosage Regimens	Criteria for Evaluation
	Moxifloxacin-	**Azithromycin-**	**Total**	• **Moxifloxacin** 400 mg PO QD x 5 days (short course) • **Azithromycin** 500 mg day 1, 250 mg PO QD x 4 days	***Efficacy*** • **Primary** - Clinical response at test of cure (14-21 days post-therapy) • **Secondary** - Patient-reported outcomes from a series of five questions 1. When did the patient begin to feel better after start of treatment? 2. When did the patient begin to return to normal activity? 3. Was the dosing schedule easy to understand? 4. Does the patient work for pay? 5. How many hours of work (from the start of treatment) did the patient miss due to illness?
Randomized	203	198	401		
ITT	201 (99.0%)	198 (100.0%)	399		
Valid for resolution*	179 (88.2%)	176 (88.9%)	355		
*In the ITT population, there were 22 indeterminate responses in each treatment group which were ineligible for the "valid for resolution" category. • The 2 treatment groups were well matched with respect to demographic variables, although a higher proportion of the moxifloxacin (88%) group had a history of smoking compared with the azithromycin group (80%)					***Safety*** Assessed on the basis of investigator-determined, drug-related adverse events

Clinical Resolution Rate

	Moxifloxacin (n = 179)	Azithromycin (n = 176)
Test of cure (14-21 days post-therapy)	152 (85%)	143 (81%)

Patient Reported Outcomes
(ITT Population Minus Missing or Indeterminate Responses)

	Moxifloxacin	Azithromycin
Reported improvement within 1-3 days of initiation of therapy	71/176 (40%)	45/165 (27%)
Mean time to patient-reported symptom relief	5.1 days*	5.8 days*
Fraction reporting symptom relief by day 3 of treatment who resulted in clinical success	64/71 (90%)	42/45 (93%)
Resumption of normal activities within the first 3 days of therapy	58/163 (36%)	41/159 (26%)

*Difference not stat. sig. using Student's t-test, but sig. at 0.05 level (P = 0.0236) using the 2-sided Wilcox test.

Hours Missed from Work (ITT Population)

Hours Missed	Moxifloxacin (n = 96)	Azithromycin (n = 93)
0	56 (58%)	50 (54%)
1-8	8 (8.3%)	16 (17.2%)
9-16	11 (11.4%)	10 (10.8%)
17-24	5 (5.2%)	3 (3.2%)
>24	16 (16.7%)	14 (15.0%)

Reduction of n is due to missing responses (105 in each group).

Drug-Related Adverse Events
(ITT Population)

Adverse Event	Moxifloxacin (n = 201)	Azithromycin (n = 198)
Any event	25 (12%)	18 (9%)
Abdominal pain	3 (1%)	3 (2%)
Digestive	14 (7%)	6 (3%)
Nausea	6 (3%)	12 (6%)
Diarrhea	6 (3%)	5 (3%)
Nervous	7 (3%)	2 (1%)
Respiratory	4 (2%)	2 (1%)

Note: events occurring in $\geq$ 1 of either group were recorded.

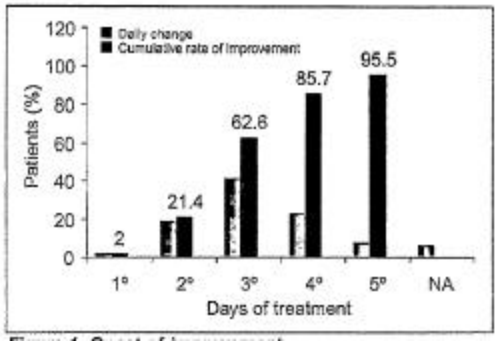
- At least 94% of patients completed the full course of therapy (193 moxifloxacin, 186 azithromycin); the rate of premature discontinuation was similar between treatment groups (5% moxifloxacin, 6% azithromycin) and was primarily due to inadequate therapeutic effect
- Premature discontinuation due to drug-related adverse events was =1% in both groups

Citation: Miravitlles M, Roz F, Cobos A, Kubin R, Tillotson G. The efficacy of moxifloxacin in acute exacerbations of chronic bronchitis: a Spanish physician and patient experience. *Int J Clin Pract*. 2001;55:437-441.

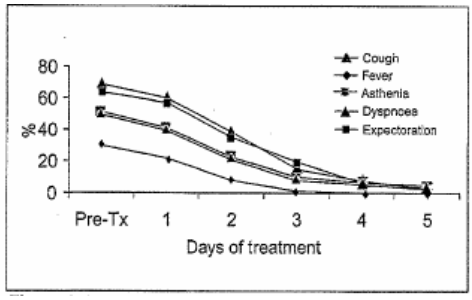
Location	Trial Design	Inclusion Criteria
Over 2000 primary care physicians in Spain	Open, community based	• Outpatients 18 years or older with acute bacterial exacerbation of bronchitis • 2 or 3 of the following presenting signs: increased sputum volume, increased sputum purulence, and increased dyspnea, in addition to productive cough

5737 Patients Enrolled, 5221 Valid for Efficacy	**Treatment and Dosage Regimens**	**Criteria for Evaluation**
• Clinical assessment at day 7 showed 93% of patients were cured • Patient diary card showed that 2/3 of patients felt better by day 3 or 4 • Adverse events were reported in 3.5% of patients, the most common being diarrhea, nausea and dizziness, and epigastric pain • Long-term follow-up at 45 days reported in 2574 patients; long-term cure rate was 97.3% (CI 94.4%-96%) •	**Moxifloxacin** 400 mg PO QD x 5 days	***Efficacy*** • **Primary** - Clinical response at 7 days and 45 days after the start of therapy ***Safety*** • **Primary** - Clinical adverse events

Onset of Improvement



Patient Assessments



Adverse Event	No. (%)
Any event	201 (3.5%)
Diarrhea	56 (1.12%)
Epigastric pain	21 (0.42%)
Dizziness	15 (0.3%)
Nausea	15 (0.2%)
Vomiting	10 (0.2)

Citation: Miravitlles M, Zalacain R, Murio C, et al. Speed of recovery from acute exacerbations of chronic obstructive pulmonary disease after treatment with antimicrobials: results of a two-year study. *Clin Drug Invest.* 2003;23:439-450.

Location	Trial Design	Inclusion Criteria
39 study centers in Spain	Multi-center, observational	• Men or women 18 years or older • Clinically stable respiratory disease in the previous month • A smoking history of at least 10 pack-years

Sample Characteristics – No. of Patients in 2 Years		Treatment and Dosage Regimens	Criteria for Evaluation
		• **Year 1:** the antimicrobial prescribed for the 1st exacerbation was maintained for all further exacerbations in year 1; choice of antimicrobial could be changed at the baseline visit for year 2 • **Year 2:** moxifloxacin 400 mg q.d. for 5 days was given to 50% of patients with ABECB	***Efficacy*** • **Primary** - Time to recovery after treatment • Clinical response was evaluated at 6-month intervals during the 2-year period; 1 year after inclusion, patients attended the 3rd visit, the baseline visit for the period when moxifloxacin was added to the treatment options
Antibiotic (total)	614		
Moxifloxacin (5.1 days)	111		
Amoxicillin/clavulanate (8.6 days)	171		
Cefuroxime (8.4 days)	83		
Clarithromycin (8.25 days)	80		
Azithromycin (n.d.)	37		
Other	132		
n.d. = not determimed.			

Results

- Mean time to recovery overall was 4.6 ± 3.3 days with moxifloxacin and 5.8 ± 4.6 days with comparators ($P < 0.01$)
- 27 patients treated with moxifloxacin in year 2 recovered in a mean of 3.7 ± 3.1 days, and the same patients treated with comparators in year 1 recovered in 6.8 ± 4.6 days ($P = 0.02$). 66 patients treated with comparators in both years, mean time to recovery was 7.4 ± 7.3 days in year 1 and 5.5 ± 3.5 days in year 2 ($P = 0.24$)
- Moxifloxacin treatment produced a statistically significant reduction of 18%-25% in the time to recovery compared with other antibiotics
- Treatment compliance was significantly better with moxifloxacin than with comparator

Citation: Miravitlles M, Llor C, Naberan K et al. Effect of various antimicrobial regimens on the clinical course of exacerbations of chronic bronchitis and chronic obstructive pulmonary disease in primary care. *Clin Drug Invest*. 2004;24:63-72.

Location	Trial Design	Inclusion Criteria	Exclusion Criteria
252 primary-care practices in Spain	Observational, non-randomized, open-label study carried out between February 2001 and May 2002	• A productive cough for at least 3 months per year for 2 consecutive years • For a diagnosis of COPD, the observation of a non-reversible airflow obstruction was required, characterized on forced spirometry by a forced volume in 1 second (FEV_1) < 80% of the theoretical value and an FEV_1/forced vital capacity (FVC) ratio of < 70% in a stable phase • Diagnosis of an exacerbation was defined by the patient's symptoms, increase in the usual level of dyspnea, increase in sputum volume, and/or increase in sputum purulence • Exacerbations having 1 of the symptoms were classified as type III, those with 2 symptoms as type II, and those with all 3 symptoms as type I. Probable bacterial etiology was established when the exacerbation was Anthonisen type I or II, or when sputum purulence was present	Patients with bronchial asthma, cystic fibrosis, bronchiectasis, malignancy or pneumonia and patients who fulfilled criteria for hospitalization were excluded.

Treatment and Dosage Regimens	Criteria for Evaluation
• **Moxifloxacin** 400 mg QD x 5 days • **Amoxicillin/clavulanic acid (co-amoxiclav)** 500 mg/125 mg tid x 10 days • **Clarithromycin** 500 mg bid x 10 days	***Efficacy*** The investigator evaluated the course of the exacerbation as a function of the resolution of the symptoms • **Primary** - The treatment was considered to have been successful if cure or clinical improvement was achieved • Cure was defined as the complete resolution of the 3 cardinal symptoms of exacerbation ***Safety*** Clinical adverse events

Severity of Exacerbations and Clinical Response to Antibacterial Therapy. (Data are expressed as percentages)

	Patients (n)	Type of Exacerbation[a] I	II	III	Clinical Success[b]	Cure Rate[c]
Co-amoxiclav	460	22.8	58	19.2	93.1	65.1
Moxifloxacin	575	22.4	61.7	15.8	97.2	67.3
Clarithromycin	421	21.7	56.9	21.4	94.4	64.0
P value[d]		0.89			0.40	0.38

Co-amoxiclav = amoxicillin plus clavulanic acid.

[a]Type of exacerbation is defined according to the Anthonisen classification.

[b]Clinical success is defined by the investigator and includes clinical cure and improvement in symptoms.

[c]Cure rate is the proportion of patients with no symptoms of exacerbation at day 10.

[d]*P* value according to the Kruskal-Wallis test.

Days to Resolution of Clinical Signs/Symptoms[a]				
Symptom	Co-Amoxiclav	Moxifloxacin	Clarithromycin	*P* Value[b]
Volume of expectoration	4.6 (2.1)	3.8 (1.7)	4.4 (2.2)	0.019
Purulence of expectoration	4.1 (2.1)	3.4 (1.7)	3.8 (2.1)	0.018
Dyspnea	4.6 (2.5)	3.8 (2.1)	4.6 (2.4)	0.21
Fever (> 38°C)	2.3 (2)	2.0 (1.7)	2.4 (2)	0.89
Cough	4.8 (2.4)	4.2 (1.6)	4.9 (2.8)	0.15

[a] Data expressed as mean (SD) number of days to resolution.

[b] Results of the comparison between the 3 groups (Kruskal-Wallis test).

Results

- The clinical cure rate, defined as the remission of the 3 cardinal symptoms of exacerbation (increased expectoration, change in sputum purulence, and increased dyspnea) were similar on the 10th day: 67% in the group receiving moxifloxacin, 65% in those taking co-amoxiclav, and 64% in those taking clarithromycin ($P = 0.38$)
- Differences in the clinical cure rates were observed on day 3 (moxifloxacin 20%, co-amoxiclav 9.6%, and clarithromycin 6.5%) and day 5 (moxifloxacin 49%, co-amoxiclav 26.5%, and clarithromycin 30%). The cure rates were significantly higher in the moxifloxacin group than in either of the other 2 treatment groups ($P < 0.001$ for both days)
- The time to resolution of symptoms was shorter in the patients in the moxifloxacin group than in the other 2 groups.

Citation: Wilson R, Kubin R, Ballin I, et al. Five day moxifloxacin therapy compared with 7 day clarithromycin therapy for the treatment of acute exacerbations of chronic bronchitis. *J Antimicrob Chemother*. 1999;44(4):501-513.

Location	Start Date and Duration	Trial Design	Inclusion Criteria	Exclusion Criteria
85 centers in Europe: Austria (2), France (26), Germany (13), Greece (3), Netherlands (6), Spain (4), Switzerland (1), UK (30)	November 22, 1996, to June 8, 1997 (1st patient's 1st visit to last patient's last visit)	Prospective, multi-national, multi-center, double-blind, randomized, 2 armed, controlled	Adults with moderate to severe ABECB including: • Patients suffering from chronic bronchitis as defined by World Health Org. criteria • At least 2 of following: ABECB symptoms: purulent/mucopurulent sputum, increasing sputum volume, increasing dyspnea (Anthonisen type I or II exacerbation)	• Known antibiotic allergy • Pregnancy or lactation • Significant renal or hepatic impairment • Concomitant serious illness • Recent antibiotic therapy • Recent participation in another clinical trial

Sample Characteristics – No. of Patients

	Moxifloxacin	Clarithro-mycin	Total
Randomized	376	373	749
ITT	374(99%)	371(99%)	745
PP	322(86%)	327(88%)	649
Valid for Microbiology	115(31%)	114(31%)	229

ITT = intent to treat; PP = per protocol.

Treatment and Dosage Regimens

- **Moxifloxacin** 400 mg PO QD x 5 days, matching placebo, including days 6 and 7
- **Clarithromycin** 500 mg PO b.i.d. x 7 days

Criteria for Evaluation

Efficacy

- **Primary** – Clinical response at day 14
- **Secondary**
  - Clinical response at end of therapy (EOT) (day 7) and at follow-up (dasy 28-35)
  - Clinical response at EOT (day 7), day 14, and at follow-up (days 28-35) in patients w/bact.-proven ABECB at start of study
  - Bact. response at EOT (day 7), day 14, and follow-up (days 28-35)

Safety

Clinical adverse events, serum biochemistry, hematology, and urinalysis

- 51 withdrawals: 32 in moxifloxacin group (23 due to adverse events) and 19 in clarithromycin group (14 due to adverse events)

Clinical Success Rate (PP Population)

Clinical Response Day 14

	Moxifloxacin (n = 322)	**Clarithromycin (n = 327)**
Clinical cure	287 (89.1%)	289 (88.4%)
Clinical failure	35 (10.9%)	38 (11.6%)

- No significant differences in clinical success rates at day 14 between moxifloxacin and clarithromycin, 95%CI (–3.9%, 5.8%)
- Same trend for clinical efficacy observed in ITT population, although, as expected, clinical success rates were slightly lower for both treatment groups
- For microbiologically valid patients, cure rates were 98/115 (85.2%) for moxifloxacin and 97/114 (85.1%) for clarithromycin

Bacteriological Success Rate

Bacteriological Response Day 7 and 14

	Moxifloxacin	**Clarithromycin**
Day 7	n=115	n=114
Success	105 (91.3%)*	78 (68.4%)*
Failure	8 (7.0%)	26 (22.8%)
Indeterminate	2 (1.7%)	10 (8.8%)
Day 14	n=115	n=114
Success	89 (77.4%)**	71 (62.3%)**
Failure	26 (22.6%)	43 (37.7%)

*95% CI (8.2%, 27.7%)

** 95% CI (3.6%, 26.9%)

Summary of Drug-Related Adverse Events by Symptoms Observed in at Least 2% of Either Treatment Group

Adverse Event	**Moxifloxacin (n = 374)**	**Clarithromycin (n = 371)**
Nausea	20 (5.3%)	15 (4.0%)
Diarrhea	11 (2.9%)	15 (4.0%)
Taste perversion	0 (0.0%)	13 (3.5%)
Dizziness	12 (3.2%)	4 (1.1%)
Headache	7 (1.9%)	10 (2.7%)
Abdominal pain	8 (2.1%)	8 (2.2%)

Citation: Wilson R, Allegra L, Huchon G, et al. Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute Exacerbations of chronic bronchitis. *Chest*. 2004;125:953-964.

Location	Trial Design	Inclusion Criteria	Exclusion Criteria
103 centers in Argentina, Australia, Austria, Belgium, Brazil, Finland, France, Germany, Greece, Hungary, Israel, Mexico, Norway, Poland , Portugal, Slovenia, Spain, Switzerland, United Kingdom	Randomized, double-blind study of 2 parallel treatment arms	Outpatients aged $\geq$ 45 years with documented chronic bronchitis (CB) were eligible for enrollment during an ABECB-free period if they had: • A history of cigarette smoking of at least 20 packs/year • Two or more documented ABECB in the previous year • FEV_1 < 85% of predicted value at enrollment visit (FEV_1: forced expiratory volume in the first second)	• Previous adverse reaction to study drugs • Pregnancy or lactation • Syndrome of QTc prolongation • Severe renal or hepatic impairment • Lung disease other than CB that could affect the clinical evaluation of study medication

Sample Characteristics – No. of Patients

	Moxifloxacin	Comparator*	Total
Randomized	357	376	733
ITT	354	376	730
PP	274	298	572
Valid for Microbio	71	79	150

ITT = intent to treat; PP = per protocol; microbio=microbiology.
*In comparator arm cefuroxime-axetil (174), clarithromycin (114), amoxicillin (88).

Treatment and Dosage Regimens

Moxifloxacin 400 mg QD x 5 days
Comparator amoxicillin 500 mg t.i.d. x 7 days, OR clarithromycin 500 mg b.i.d. x 7 days, OR cefuroxime axetil 250 mg b.i.d. x 7 days

Criteria for Evaluation

Efficacy

- **Primary** – Clinical response 7-10 days post-therapy
- **Other**
  - Further antimicrobial use
  - Time to next ABECB
  - Bacteriological success

Safety

Clinical adverse events

Clinical Efficacy Results (7-10 Days Post-Therapy)

	ITT Population			PP Population		
	Moxifloxacin No./n (%)	Comparator No./n (%)	95% CI	Moxifloxacin No./n (%)	Comparator No./n (%)	95% CI
Clinical success[a,b]	310/354 (87.6)	312/376 (83.0)	[–0.7, 9.5]	239/274 (87.2)	251/298 (84.2)	[–3.0, 8.5]
Clinical cure	251/354 (70.9)	236/376 (62.8)	[1.4, 14.9]	191/274 (69.7)	185/298 (62.1)	[0.3, 15.6]
Clinical success in patients w/bact. confirmed ABECB[a]	98/112 (87.5)	94/120 (78.3)	[–1.4, 17.9]	62/71 (87.3)	66/79 (83.5)	[–7.2, 15.4]

[a]Clinical cure and improvement combined.
[b]In ITT pop. clinical success rates in amoxicillin, clarithromycin, and cefuroxime axetil groups were, respectively, 83.0%, 84.2%, and 82.2%; in per-protocol pop. corresponding figures were 81.5%, 87.4%, and 83.8%

Bacteriological Response (7-10 Days Post-Therapy)

	ITT Pop.		Microbio Valid Pop.	
	Moxi No. (%)	Comp No. (%)	Moxi No. (%)	Comp No. (%)
Total	112 (100.0)	120 (100.0)	71 (100.0)	79 (100.0)
Bacteriological Success	86 (76.8)	81 (67.5)	65 (91.5)	64 (81.0)
Eradication	42 (37.5)	39 (32.5)	36 (50.7)	35 (44.3)
Presumed eradication	44 (39.3)	42 (35.0)	29 (40.8)	29 (36.7)
Bacteriological failure	26 (23.2)	39 (32.5)	6 (8.4)	15 (19.0)
Erad. w/ superinfect.	3 (2.7)	4 (3.3)	3 (4.2)	4 (5.1)
Persistence[c]	7 (6.3)	15 (12.5)	3 (4.2)	11 (13.9)

[c]Includes persistence w/superinfection; Comp = comparator.

Incidence of More Frequent Drug-Related Adverse Events[d]

Adverse Event	**Moxifloxacin (n = 354)**	**Comparator (n = 376)**
Any adverse event	25 (7.1%)	18 (4.8%)
Abdominal pain	3 (0.8%)	2 (0.5%)
Headache	4 (1.1%)	3 (0.8%)
Diarrhea	9 (2.5%)	3 (0.8%)
Gastritis	2 (0.6%)	–
Nausea	3 (0.8%)	2 (0.5%)
Dizziness	3 (0.8%)	–
Nervousness	2 (0.6%)	–
Taste perversion	–	3 (0.8%)

[d]At least 2 patients reporting a possibly or probably drug-related adverse event.

Section 2.1.a.4
Pivotal Safety and Efficacy Trials – Skin and Skin Structure Infections

Citation: Parish LC, Routh HB, Miskin B, et al. Moxifloxacin versus cephalexin in the treatment of uncomplicated skin infections. *Int J Clin Pract*. 2000;54(8):497-503.

Location	Start Date and Duration	Trial design	Inclusion Criteria
32 centers in United States	August 20, 1997, to May 5, 1998 (1st patient's 1st visit to last patient's last visit)	Prospective, controlled, randomized, multi-center, double-blind	Male and female outpatients aged 18 years or older with acute uncomplicated skin and superficial skin structure infections

Sample Characteristics – No. of Patients				Treatment and Dosage Regimens	Criteria for Evaluation
	Rx1	**Rx2**	**Total**	• **Rx1:** moxifloxacin 400 mg PO QD x 7 days • **Rx2:** cephalexin 500 mg PO t.i.d. x 7 days	***Efficacy*** • **Primary** – Clinical response 7-21 days post-therapy • **Secondary** – Clinical and bacteriological response during therapy (days 3-4), as well as bacteriological response 7-21 days post-therapy ***Safety*** Physical examination findings, adverse events, intercurrent illness, ECG, premature discontinuation of treatment, concomitant medication use, and lab tests results including hematology blood chemistry, urinalysis, and theophylline if indicated
Randomized	201	200	401		
ITT population	201	198	399		
PP population	180	171	351		
Valid for Microbiology	68	57	125		
ITT = intent to treat (valid for safety); PP = per protocol (valid for efficacy).					

- The type of acute skin or superficial skin structure infections treated in this trial were cellulitis, impetigo, operative wound, trauma, erysipleoid, simple abscesses, and others

Clinical Response Rates
(7-21 Days Post-Therapy)

	Moxifloxacin	Cephalexin
Per Protocol (PP)	**180**	**171**
Resolution	162 (90%)	155 (91%)
Improvement	0 (0%)	1 (0.5%)
Failure	18 (10%)	15 (9%)
Indeterminate	0 (0%)	0 (0%)
Intent to Treat (ITT)	**201**	**198**
Resolution	169 (84%)	166 (84%)
Improvement	0 (0%)	1 (0.5%)
Failure	20 (10%)	16 (8%)
Indeterminate	12 (6%)	15 (7.5%)

Bacteriological Response Rate

	Moxifloxacin	Cephalexin
10-14 days post-treatment	91%	91%

- The bacteriological response rates (eradication/presumed eradication) 10-14 days post-treatment for the major infecting organisms, *S. aureus* and *Streptococcus* species, was 92% and 93%, respectively, in the moxifloxacin treatment group and 90% and 82%, respectively, in the cephalexin treatment group

Summary of Adverse Events (ITT Population)

Adverse Events (AEs)	Moxifloxacin (n = 201)	Cephalexin (n = 198)
Any adverse event	67 (33%)	67 (34%)
Any drug-related AE	42 (21%)	37 (19%)
Any serious event	7 (3%)	8 (3%)
Discontinuation due to AE	6 (3%)	7 (4%)

Summary of Adverse Events by Symptoms Observed in At Least 2% of Either Treatment Group

Body System	Moxifloxacin (n = 201)	Cephalexin (n = 198)
Any event	42 (21%)	37 (19%)
Abdominal pain	6 (3%)	3 (2%)
Headache	5 (2%)	6 (3%)
Nausea	12 (6%)	6 (3%)
Diarrhea	7 (3%)	5 (3%)
Rash	3 (1%)	3 (2%)
Pruritus	1 (<1%)	3 (2%)

- Serious or life-threatening events occurred more frequently in cephalexin group (6 vs 1)

Citation: Wise R, Andrews JM, Marshall G, Hartman G**.** Pharmacokinetics and inflammatory-fluid penetration of moxifloxacin following oral or intravenous administration**.** *Antimicrob Agents Chemother*. 1999;43:1508-1510.

Location	Trial Design	Inclusion Criteria
United Kingdom	8 healthy male volunteers	• Healthy males between 26-41 years • No history of serious illness, atopy, alcohol or drug abuse, or any acute illness in the 14 days prior to the start of the study • Subjects had not received any prescribed or over-the-counter medication in the 14 days prior to the first dose

Treatment and Dosage Regimens	Criteria for Evaluation
• Each volunteer received 400 mg oral or IV moxifloxacin (administered over 1 h) in a random order, and 6 weeks later, received the agent by the other route • Blister formation was induced the evening prior to the study by 0.2% cantharidin-impregnated patches attached to the forearm	***Efficacy*** • **Primary** – Clinical response at 3-5 days post-Tx • **Secondary** – Clinical response at 21-28 days post-Tx, bacteriological response 3-5 days and 21-28 days post-Tx, clinical and bacteriological response 3-5 days post-start of Tx ***Safety*** Clinical adverse reactions, standard lab assessments, and clinical variables
• In the PP and ITT populations, the 3 treatment groups were comparable on age, sex, weight and BMI, and concomitant medication. • No significant differences with regard to baseline signs and symptoms of community-acquired pneumonia	

Results

- The mean maximum concentrations observed in plasma were 4.98 mg/mL after oral dosing and 5.09 mg/mL after IV dosing
- Mean maximum concentrations attained in inflammatory fluid were 2.62 and 3.23 mg/mL for oral and IV dosing, respectively
- Mean elimination half-lives from plasma were 8.32 and 8.17 h, respectively
- Overall penetration into the inflammatory fluid was 103.4% and 104.2% for oral and IV routes, respectively
- Over 24 h, 15% of the drug was recovered in the urine when administered by either route

Citation: Data on File. Study 100273/MRR-00082. Schering Corporation. Kenilworth, New Jersey.

Location	Start Date and Duration	Trial design	Inclusion Criteria
68 centers in 6 countries (United States -47, Canada - 14, Israel - 2, Chile - 2, Argentina - 2, and Peru - 1)	December 12, 2000 to July 20, 2003 (1st patient's 1st visit to last patient's last visit)	Prospective, randomized, active- control, double-blind, multi-center	Male and female patients aged 18 years or older who were hospitalized with a diagnosis of complicated skin and skin structure infections requiring initial inpatient IV antimicrobial therapy.

Sample Characteristics – No. of Patients

	Moxi	Comp	Total
Randomized	306	311	617
ITT population	298	303	601
PP population	180	187	367
Valid for Microbiology	119	118	237

ITT = intent to treat (valid for safety); PP = per protocol (valid for efficacy).

Treatment and Dosage Regimens

- **Rx1:** IV/PO moxifloxacin 400 mg QD
- **Rx2:** IV piperacillin/ tazobactam 3.0 g/ 0.375 g Q6H followed by PO amoxicillin/ clavulanic acid suspension 800 mg Q12H

IV treatment was administered for a minimum of 3 days and combined IV/PO treatment duration was 7 to 14 days.

Criteria for Evaluation

Efficacy

- **Primary** – Clinical response at test of cure (TOC), 10-42 days after the last dose of study drug.
- **Secondary** – Bacteriological success at the TOC, clinical and bacteriological responses on the day of IV to PO switch or on treatment day 3-5 (if the day of switch was other than day 3, 4, or 5), mortality attributed to cSSSI at the TOC, days of hospitalization, days of hospitalization postoperatively (if applicable), and days of IV therapy.

Safety

Monitoring for adverse events, ECG, and laboratory tests including hematology, chemistry, urinalysis, urine and serum pregnancy testing.

- The type of complicated skin or superficial skin structure infections treated in this trial included infected ischemic ulcer or decubitus ulcer, diabetic foot infections, abscesses, cellulitis (including cellulitis with lymphedema and cellulitis with venous stasis), surgical wound infection, complicated erysipelas, infection with traumatic lesion (infection of traumatic lesion, bite wound infection, and infection with trauma), and other infection types (hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infection, infection of deep soft tissue and lymphangitis).

Clinical Response Rates
(10-42 days after the last dose of study drug)

	Moxifloxacin	Comparator
Per Protocol (PP)	**180**	**187**
Overall Cure Rate	143 (79.4%)	153 (81.8%)
Cure	142 (78.9%)	153 (81.8%)
Resolution	1 (0.6%)	0 (0%)
Failure	37 (20.6%)	34 (18.2%)
Intent to Treat (ITT)	**298**	**303**
Overall Cure Rate	166 (55.7%)	169 (55.8%)
Cure	164 (55.0%)	168 (55.4%)
Resolution	2 (0.7%)	1 (0.3%)
Failure	43 (14.4%)	48 (15.6%)
Indeterminate	22 (7.4%)	21 (6.9%)
Missing	67 (22.5%)	65 (21.5%)

Clinical Response by Infection Type at the TOC (PP population)

	Moxifloxacin (n=180)	Comparator (n=187)
Abscess	42/53 (79%)	52/56 (93%)
Cellulitis	36/43 (84%)	38/43 (88%)
Diabetic foot infection	25/37 (68%)	25/41 (61%)
Infected ischemic ulcer or decubitus ulcer	10/13 (77%)	6/10 (60%)
Surgical wound infection	11/12 (92%)	8/8 (100%)
Complicated erysipelas	-	2/2 (100%)
Infection with traumatic lesion	11/12 (92%)	10/13 (77%)
Other infection types	8/10 (80%)	12/14 (86%)

Bacteriological Response Rate at TOC in the PP population

	Moxifloxacin (n=119)	Comparator (n=118)
Overall Eradication Rate	92 (77.3%)	96 (81.4%)
Eradication	2 (1.7%)	2 (1.7%)
Presumed Eradication	90 (75.6%)	94 (79.7%)
Persistence	2 (1.7%)	4 (3.4%)
Presumed Persistence	25 (21.0%)	18 (15.3%)

- For all infection types, *Staphylococcus aureus* was the most frequently isolated organism.

Summary of Adverse Events (ITT Population)

Adverse Events (AEs)	Moxifloxacin (n = 298)	Comparator (n = 303)
Any adverse event	223 (74.8%)	218 (71.9%)
Any drug-related AE	93 (31.2%)	91 (30.0%)
Any serious event	41 (13.8%)	44 (14.5%)
Discontinuation due to AE	27 (9.1%)	31 (10.2%)
Death	3 (1.0%)	3 (1.0%)

- One death in each treatment group was assessed to be drug related (Clostridium colitis in the moxifloxacin group and cardiorespiratory arrest in the comparator group.

Summary of Adverse Events by Symptoms Observed in At Least 3% of Either Treatment Group (ITT Population)

Body System	Moxifloxacin (n = 298)	Comparator (n = 303)
Any event	223 (75%)	218 (72%)
Anemia	22 (7%)	10 (3%)
Nausea	33 (11%)	20 (7%)
Constipation	27 (9%)	14 (5%)
Diarrhea	23 (8%)	34 (11%)
Vomiting	14 (5%)	9 (3%)
Dyspepsia	5 (2%)	11 (4%)
Pyrexia	16 (5%)	11 (4%)
Cellulitis	10 (3%)	12 (4%)
Alanine aminotransferase increased	9 (3%)	7 (2%)
Gamma glutamyl transferase increased	7 (2%)	10 (3%)
Hypokalemia	11 (4%)	14 (5%)
Pain in extremity	8 (3%)	11 (4%)
Headache	24 (8%)	29 (10%)
Insomnia	38 (13%)	33 (11%)
Anxiety	13 (4%)	5 (2%)
Pruritis	9 (3%)	10 (3%)
Hypertension	11 (4%)	8 (3%)

- 41 subjects in the moxifloxacin treated group reported at least 1 serious adverse event. Five serious adverse events in 4 patients were assessed as related to moxifloxacin therapy.
- 44 subjects in the comparator treated group reported at least 1 serious adverse event. Ten events in 9 patients were assessed as related to comparator drug therapy.

Citation: Data on File. Study 10279/MRR-00133. Schering Corporation. Kenilworth, New Jersey.

Location	Start Date and Duration	Trial design	Inclusion Criteria
74 centers in 12 countries (Philippines – 4, Taiwan – 2, Germany – 6, Hungary – 5, Spain – 5, Israel – 5, Argentina – 4, Chile – 8, Colombia – 2, Mexico – 25, Peru – 4, South Africa – 4)	April 03, 2001 to April 08, 2002 (1st patient's 1st visit to last patient's last visit)	Prospective, randomized, non-blinded, comparative with parallel groups, multi-center and multi-national	Male and female patients aged 18 years or older who presented with complicated skin and skin structure infection (cSSSI) of <21 days duration, only one site of skin and skin structure infection, and required systemic antimicrobial treatment.

Sample Characteristics – No. of Patients

	Moxi	Comp	Total
Randomized	406	398	804
ITT population	406	397	803
PP population	315	317	632
ITT/MBE	219	208	427
PP/MBE	167	172	339

ITT = intent to treat (valid for safety); PP = per protocol (valid for efficacy); MBE = microbiologically evaluable.

Treatment and Dosage Regimens

- **Rx1:** IV/PO moxifloxacin 400 mg QD
- **Rx2**: IV amoxicillin/ clavulanate* 1.0 g/200 mg TID followed by PO amoxicillin/ clavulanate 500 mg/125 mg TID

IV treatment was administered for a minimum of 3 days and combined IV/PO treatment duration was 7 to 21 days.

Criteria for Evaluation

Efficacy

- **Primary** – Clinical response at day 14 to 28 after the end of treatment (Test of Cure, TOC).
- **Secondary** – Clinical and bacteriological response on day 3 of treatment, bacteriological response at TOC, incidence of sepsis, incidence of nosocomial infections in relation to length of hospitalization, number of days of hospitalization in both treatment regimens, major healthcare resources used from day 1 to days 14 to 28 after the end of study treatment, and clinical response at TOC for the individual diagnosis.

Safety

Based on physical examinations, laboratory tests (hematology, clinical chemistry, urinalysis, blood gases), and the reporting of adverse events.

- The type of complicated skin or superficial skin structure infections treated in this trial included diabetic foot infection, necrotizing fascitis, moderate to severe wound infections, complicated erysipelas, spontaneous or traumatic major abscesses of the skin, acute infected traumatic lesions of the skin and soft tissues, infected ischemic ulcers, and cellulitis.

* IV amoxicillin clavulanate is not FDA approved.

Clinical Response Rates
(10-42 days after the last dose of study drug)

	Moxifloxacin	Comparator
Per Protocol (PP)	**315**	**317**
Success	254 (80.6%)	268 (84.5%)
Intent to Treat (ITT)	**406**	**397**
Success	295 (72.7%)	297 (74.8%)

Clinical Response at TOC (PP population) Analyzed by Primary Diagnosis

Abscess	n=98	n=93
Cure	93.9%	88.2%
Failure	6.1%	11.8%
Fascitis	n=22	n=13
Cure	50.0%	53.8%
Failure	50.0%	46.2%
Surgical Wound Infection	n=9	n=13
Cure	88.9%	92.3%
Failure	11.1%	7.7%
Diabetic Foot Infection	n=49	n=63
Cure	51.0%	66.7%
Failure	49.0%	33.3%
Infected Ischemic Ulcers	n=6	n=4
Cure	33.3%	100.0%
Failure	66.7%	0.0%
Complicated erysipelas	n=101	n=95
Cure	90.1%	94.7%
Failure	9.9%	5.3%
Infection of traumatic lesion	n=21	n=19
Cure	81.0%	84.2%
Failure	19.0%	15.8%
Cellulitis	n=9	n=17
Cure	88.9%	88.2%
Failure	11.1%	11.8%

Bacteriological Response Rate at TOC in the PP population

	Moxifloxacin (n=167)	Comparator (n=172)
Success (eradication + presumed eradication)	127 (76.0%)	140 (81.4%)

Bacteriological Response Rate at TOC in the ITT population

	Moxifloxacin (n=219)	Comparator (n=208)
Success (eradication + presumed eradication)	147 (67.1%)	144 (69.2%)

- *Staphylococcus aureus* was the most frequently isolated gram positive organism and *Escherichia coli* was the most commonly isolated gram negative organism.

Summary of Adverse Events (ITT Population)

Adverse Events (AEs)	Moxifloxacin (n = 406)	Comparator (n = 397)
Any adverse event	211 (52%)	190 (48%)
Any drug-related AE	72 (18%)	64 (16%)
Any serious event	57 (14%)	45 (11%)
Discontinuation due to AE	25 (6%)	15 (4%)
Death	8 (2%)	3 (1%)

- No deaths were reported to be study related but were judged to be due to the patient's underlying conditions.
- The majority of serious adverse events were linked to the medical condition of the subjects enrolled.
- Nine out of the 102 events were assessed as drug related (moxifloxacin, n=6; comparator, n=3).
- The 6 serious events in the moxifloxacin group judged to be drug related included volvulus, hepatic function abnormal NOS, jaundice NOS, colitis pseudomembranous, atopic dermatitis, and assessment of ineffective drug.
- In the comparator treated group, the serious adverse events identified to be drug related included two cases of cellulitis and once case of infection aggravated NOS.

Summary of Adverse Events by Symptoms Observed in =2% of Either Treatment Group (ITT Population)

Body System	Moxifloxacin (n = 406)	Comparator (n = 397)
Blood and lymphatic system disorder	30 (7.4%)	24 (6.0%)
Anemia NOS	11 (2.7%)	7 (1.8%)
Cardiac disorders	12 (3.0%)	12 (3.0%)
Gastrointestinal disorders	49 (12.1%)	42 (10.6%)
Diarrhea NOS	18 (4..4%)	18 (4.5%)
Nausea	17 (4.2%)	11 (2.8%)
Vomiting NOS	13 (3.2%)	9 (2.3%)
Administration site conditions	24 (5.9%)	22 (5.5%)
Pyrexia	9 (2.2%)	5 (1.3%)
Infections and Infestations	48 (11.8%)	41 (10.3%)
Septic Shock	8 (2.0%)	3 (0.8%)
Investigations	34 (8.4%)	38 (9.6%)
GGT increased	8 (2.0%)	10 (2.5%)
LDH increased	6 (1.5%)	10 (2.5%)
AST increased	8 (2.0%)	7 (1.8%)
Metabolism and Nutrition Disorders	27 (6.7%)	17 (4.3%)
Hyperglycemia NOS	10 (2.5%)	4 (1.0%)
Hypoglycemia NOS	8 (2.0%)	5 (1.3%)
Musculoskeletal and connective tissue disorders	14 (3.4%)	10 (2.5%)
Nervous System disorders	30 (7.4%)	21 (5.3%)
Headache NOS	14 (3.4%)	17 (4.3%)
Dizziness (excluding vertigo)	10 (2.5%)	1 (0.3%)
Psychiatric disorders	8 (2.0%)	10 (2.5%)
Renal and urinary disorders	25 (6.2%)	11 (2.8%)
Hematuria	8 (2.0%)	1 (0.3%)
Respiratory, thoracic, and mediastinal disorders	15 (3.7%)	12 (3.0%)
Skin and subcutaneous tissue disorders	17 (4.2%)	16 (4.0%)
Surgical and medical procedures	18 (4.4%)	24 (6.0%)
Toe amputation	8 (2.0%)	12 (3.0%)
Vascular disorders	32 (7.9%)	20 (5.0%)

NOS=Not otherwise specified

2.1.b Prospective Effectiveness Trials

A summary of the following study is contained in this subsection:

- Landen H, Bauer T. Efficacy, onset of action and tolerability of moxifloxacin in patients with community-acquired pneumonia. *Clin Drug Invest*. 2001;21(12):801-811.

Citation: Landen H, Bauer T. Efficacy, onset of action and tolerability of moxifloxacin in patients with community-acquired pneumonia. *Clin Drug Invest*. 2001;21(12):801-811.

Location	Start Date and Duration	Trial Design	Inclusion
410 hospitals throughout Germany	September 13, 1999, to March 31, 2001	Post-marketing surveillance study	Patients admitted to the hospital with CAP who had been prescribed moxifloxacin as the most appropriate therapy

Demographics of Patients

Age (years)

< 39	40-59	60-79	> 80
8.8%	20%	51.2%	20%

Sex

Male	Female	Unknown
1239(56.6%)	940(43.0%)	9(0.4%)

Smokers

Yes	Former
29.9%	13.0%

Disease Severity

Severe	Moderate	Mild
29.0%	59.4%	11.3%

- The majority of patients (88.6%) had at least 1 other illness and most had 2 or more; prior to therapy, the most common concomitant diseases were 60.1% cardiovascular, 35.9% respiratory, 26.9% diabetes

Treatment and Dosage Regimens

All Moxifloxacin

- **> 99% 400 mg, q.d. p.o.**
- **0.2% 800 mg, q.d. p.o.**
- **0.6% unknown**

Tx Duration

< 5 days	**3.7%**
5-10 days	**78.0%**
> 10 days	**17.1%**

Mean 8.6 days ± 2.9

Criteria for Evaluation

Efficacy

Primary – **Characterize the profile of the onset of action of moxifloxacin with regard to clinical improvement and cure.**

Patients followed over entire course of Tx as well as post-Tx period until discharge. Following symptoms assessed and recorded on each day of moxifloxacin treatment: body temp, heart rate, coughing, expectoration, sputum, dyspnea, thoracic pain, responsiveness/orientation, and auscultation

Safety

The onset, nature and duration of all adverse events reported during the study period were recorded, irrespective of causal relationship

Summary of Clinical Efficacy

- The severity of the principal clinical symptoms was documented by physician was recorded for:
  80% of patients on each of the first 5 days
  66% of patients on each of the first 10 days
- CAP symptoms fell rapidly after only 3 days of treatment

- 93.4% of patients were cured or improved after treatment
- 60.4% demonstrated distinct improvement after 3 days
- 90% were improved by day 5
- 50% were symptom free by day 5
- 73.7% were symptom free by day 7
- 87.0% were symptom free by day 10

Summary of Adverse Events

Adverse Events (Es)	Moxifloxacin (N = 2188)	
Any adverse event	105	4.8%
Any drug-related AE	59	2.7%
Any serious adverse event (SAE)	42	1.9%
Any drug-related SAE	13	0.6%

- Overall, the tolerability of moxifloxacin therapy was rated as "very good" or "good" by 96% of physicians

The profile of AEs was similar to that previously reported for moxifloxacin, mostly involving gastrointestinal disturbances and skin rash

Summary of Adverse Events by Symptoms

Adverse Event	Moxifloxacin (N = 2188)
Diarrhea	29 (1.3%)
Cardiac events (8 patients, 10 events)	10
Transient hypotension (treatment related)	1
Heart failure	3
Myocardial infarct	2
Angina pectoris	1
Sudden death	1
Tachycardia	1
Ventricular fibrillation	1
Hepatic events (8 patients, 10 events)	8
Transient abnormal liver function tests	7
Prolonged abnormal liver function tests	1
Therapy prematurely withdrawn due to AEs	34 (1.6%)

2.1.c Prospective Studies Examining Non-Economic Endpoints

No applicable studies.

2.1.d Retrospective Studies

No applicable studies.

2.1.e Review Articles and Meta-Analyses

No applicable studies.

2.1.f Spreadsheet of All Published and Unpublished Trials

A spreadsheet summarizing the published and unpublished trials presented above is contained in this subsection on the following pages.

Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Community Acquired Pneumonia

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Faich GA, Morganroth J, Whitehouse AB, et al. Clinical experience with moxifloxacin in patients with respiratory tract infections. *The Annals of Pharmacotherapy.* 2004;38:749-754.	Study enrollment was conducted between April 10 and June 26,2000.	Large post-marketing safety and efficacy study	Moxifloxacin 400 mg PO QD x 10 days for ABS or CAP Moxifloxacin 400 mg PO QD x 5 days for ABECB	Safety Total – 18,374 ABS – 10,822 ABECB – 6,039 CAP – 1,387 Efficacy Total – 17,137 ABS - 10,065 ABECB – 5,664 CAP – 1,298	Inclusion Subjects ≥ 18 years of age, not hospitalized, clinical diagnosis of ABS, ABECB, or mild to moderate CAP Exclusion Currently taking class IA or III antiarrhythmics, has prolongation of QT interval, history of hypersensitivity to quinolones, pregnant, lactating, concomitant systemic antimicrobial use during the study	Safety Assessed by an independent external safety committee specializing in cardiology and drug safety. AEs recorded were signs and symptoms, study drug relationship, ECG tracings if performed, cardiac history, recent electrolyte, renal, and hepatic function. Efficacy Clinical success (clinical cure plus improvement)	Safety AEs for all patients: 14.3% (n=2635) ABS: 16.6% (n=1793) ABECB: 10.7% (n=646) CAP: 13% (n=181) Possible cardiac AE: 1.6% Efficacy Total clinical success: 92.9% (n=15,924) ABS: 92.8% (n=9337) ABECB: 92.9% (n=5263) CAP: 94.1% (n=1222)
File TM Jr, Larsen LS, Fogarty CM, et al. Safety and efficacy of sequential (IV to PO) moxifloxacin for the treatment of community-acquired pneumonia in hospitalized patients. *Today's Ther Trends.* 2001;19(4):251-270.	Not given	Prospective, randomized, double-blind, double-dummy	Moxifloxacin Sequential IV/PO 400 mg QD Comparator Initially IV alatrofloxacin/PO trovafloxacin 200 mg QD, changed to IV/PO levofloxacin 500 mg QD after concerns about hepatotoxicity Each subject received a total of 7-14 days of IV/PO therapy	Efficacy Total–356 Moxifloxacin–177 Comparator–179 Safety Total–507 Moxifloxacin–249 Comparator–258 Microbiology Valid Total–152 Moxifloxacin–75 Comparator–77	Inclusion Subjects ≥ 18 years with mild to moderate or severe CAP requiring IV therapy Patients having fever (≥ 38°C [oral]; > 38.5°C [tympanic]; or > 39°C [rectal]) and/or elevated white blood cell count (WBC) count (≥ 12,000/mm^3), total WBC count < 4500/mm^3, or ≥ 15% immature neutrophils At least one of the following: productive cough, purulent sputum, dyspnea, or tachypnea [> 20 breaths/min], rigor/chills, pleuritic chest pain, or signs of pulmonary consolidation New or progressive infiltrate on chest x-ray confirmed by radiologist	Efficacy Clinical response (cure, failure, or indeterminate) at test-of-cure visit (7-30 days post-therapy) Clinical response as related to infecting pathogen was also determined for microbiologically valid population Safety Assessed by clinical observation and conventional lab tests. AEs rated by the investigator as to their severity and relationship to the study drug	Clinical Response Clinical resolution at TOC (7-30 days post Tx) for moxifloxacin 88%; specifically, in mild/moderate cases was 92% and in severe cases was 79%. For the comparator–89%, specifically, in mild/moderate cases 93% and in severe cases 80%. Safety Incidence rate of drug-related AEs for Moxifloxacin were 39% and for Comparator, 40%

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Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Finch R, Schürmann D, Collins O, et al. Randomized controlled trial of sequential intravenous (i.v.) and oral moxifloxacin compared with sequential i.v. and oral co-amoxiclav with or without clarithromycin in patients with commun ity-acquired pneumonia requiring initial parenteral treatment. *Antimicrob Agents Chemother*. 2002;46(6):1746-1754.	Not given	Multi-national, multi-center, randomized, open, parallel-group	Moxifloxacin 400 mg IV QD followed by 400 mg PO for 7 to 14 days Comparator Co-amoxiclav 1200 mg IV t.i.d. followed by co-amoxiclav 625 mg PO t.i.d. with or without clarithromycin 500 mg b.i.d. (IV or PO) for 7 to 14 days	Efficacy Total–538 Moxifloxacin–258 Comparator–280 Safety Total–622 Moxifloxacin–301 Comparator–321	Inclusion Males and females aged 18 years and over with radiological evidence of CAP, in hospital <48 hours Having temp ≥ 38.5 °C or leukocytosis and ≥ 1 of following: pneumonia including cough, purulent sputum, dyspnea, rigors, pleuritic chest pain, or auscultatory findings All patients required initial parenteral therapy and approximately half had severe pneumonia, as defined by the criteria of the American Thoracic Society	Efficacy Primary – Clinical response (cure, failure, or indeterminate) at t est of cure (TOC) visit (5-7 days after end of therapy) Secondary – Time to resolution of fever, bact. response 5 to 7 days after treatment, bact. and clinical responses 21 to 28 days post-treatment, duration of IV therapy, and duration of hospital admission Safety Assessed by incidence rate of adverse events, lab data, and ECG findings	Efficacy Clinical cure at TOC: Moxifloxacin–93.4% Comparator–85.4% Clinical cure at follow up: Moxifloxacin–83.7% Comparator–74.3% Bact. Success at TOC: Moxifloxacin–93.7% Comparator–81.7% (p=0.004) Bact. Success at follow up: Moxifloxacin–84.4% Comparator–70.4% Safety Incidence rate of drug-related AEs Moxifloxacin–38.9% Comparator–38.9%

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Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Data on File. Study 10872/MRR-00140. Schering-Plough Corporation. Kenilworth, New Jersey.	November 2002 to April 2004	Prospective, randomized controlled, double-blind, double-dummy, multi-center, comparative study	Moxifloxacin 400 mg IV/PO QD Comparator Levofloxacin 500 mg IV/PO QD Both treatment groups were treated for a total of 7-14 days	Efficacy Total–281 Moxifloxacin–141 Comparator–140 Safety Total–394 Moxifloxacin–195 Comparator–199	Hospitalized elderly patients (=65 years), requiring initial IV therapy, radiologically-confirmed evidence of a new or progressive infiltrate, and =2 of the following: productive cough w/ purulent or mucopurulent sputum; tracheobronchial secretions or change in character of sputum; dyspnea or tachypnea; rigors or chills; pleuritic chest pain; auscultatory findings on pulmonary examination of rales/crackles and/or evidence of pulmonary consolidation; fever or hypothermia; and white blood cell count =10,000/mm^3, or =15% immature neutrophils (bands), regardless of the peripheral WBC count or leukopenia with a total WBC count <4500/mm^3.	Efficacy Primary – Clinical at test of cure (TOC) visit (5-21 days post-therapy) Secondary – Clinical response at the during therapy (day 3-5) visit and bacteriologic response at the TOC visit. Health resource utilization assessment – Collected at the TOC visit and included length of hospital stay, length of stay in an intensive care unit (ICU), total days of antimicrobial therapy, and duration of IV therapy. Safety Assessed by adverse events, lab data, and chest X-ray.	Efficacy Clinical cure at TOC: Moxifloxacin–92.9 Comparator–87.9 Clinical cure for the microbiologically valid: Moxifloxacin–81.0% Comparator–76.7% Bact. Success at TOC: Moxifloxacin–81.0% Comparator–75.0% Safety Incidence rate of drug-related AEs Moxifloxacin–26.2% Comparator–22.6%

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Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Fogarty C, Grossman C, Williams J, et al. Efficacy and safety of moxifloxacin vs clarithromycin for community-acquired pneumonia. *Infect Med*. 1999;16:748-763.	November 1996 to May 1998 (1st patient's 1st visit to last patient's last visit)	Prospective, multi-center, randomized, double-blind	Moxifloxacin 400 mg PO QD Clarithromycin 500 mg PO b.i.d. Both treatments given for 10 days	Efficacy Total–382 Moxifloxacin–194 Clarithromycin–188 Safety Total–473 Moxifloxacin–237 Clarithromycin–236 Microbiologically Valid Total–214 Moxifloxacin–110 Clarithromycin–104	Inclusion Men or women 18 years or older with fever (temp > 38°C) and/or leukocytosis At least one of following: productive cough, purulent sputum, dyspnea or tachypnea, rigor/chills, pleuritic chest pain, and ausculatory findings such as rales/rhonchi and/or evidence of pulmonary consolidation Radiological evidence of new or progressive infiltrate consistent w/pneumonia	Efficacy Primary – Clinical response at follow-up (day +24 to +45) Secondary – Clinical response at EOT (day +2 to +4) and bacteriological response at EOT (end of therapy) and follow-up Safety Physical examination, ECGs, adverse events, intercurrent illness, and lab tests such as hematology, blood chemistry, urinalysis, and theophyline (if indicated)	Efficacy Clinical resolution at EOT: Moxifloxacin–97% Clarithromycin–95% Overall clinical resolution: Moxifloxacin–95% Clarithromycin–95% Microbiological response at EOT and follow–up: Moxifloxacin–97%, 94% Clarithromycin–96%, 93% Safety Drug related AEs were experienced by 35% patients in moxifloxacin group and 34% in clarithromycin group
Hoeffken G, Meyer HP, Winter J, et al. The efficacy and safety of two oral moxifloxacin regimens compared to oral clarithromycin in the treatment of community-acquired pneumonia. *Respir Med.* 2001;95:553-564.	November 26, 1996 to February 5, 1998 (1st patient's 1st visit to last patient's last visit)	Prospective, multi-national, multi-center, randomized, 3 armed, active-controlled, double-blind	Rx1: Moxifloxacin 200 mg PO QD Rx2: Moxifloxacin 400 mg PO QD Rx3: Clarithromycin 500 mg PO b.i.d. All three treatments given for 10 days with water before or with meal	Efficacy Total–531 Rx1–180 Rx2–177 Rx3–174 Safety Total–675 Rx1–229 Rx2–224 Rx3–222	Inclusion Patients of either sex who were at least 18 years with fever (core temp > 38.5°C or oral temp > 38°C) and/or leukocytosis ≥ 1 of following: productive cough, purulent sputum, dyspnea or tachypnea, rigor/chills, pleuritic chest pain, and rales/rhonchi indicating consolidation Radiological evidence of new or progressive infiltrate consistent w/pneumonia	Efficacy Primary – Clin resp at 3-5 d post-Tx Secondary – Clin resp 21-28 d post-Tx, bact resp 3-5 d and 21-28 d post-Tx, clin and bact resp 3-5 d post-start of Tx Safety Clinical adverse reactions, standard lab assessments, and clinical variables	Efficacy Clinical cure rate at EOT and follow-up: Rx1–93.9%, 90.7% Rx2–94.4%, 92.8% Rx3–94.3%, 92.2% Bacteriological response at EOT and at follow-up: Rx1–72.5%, 62.5% Rx2–78.7%, 53.2% Rx3–70.7%, 68.3% Safety Incidence rate of drug-related AEs Rx1 – 35.8% Rx2 – 37.5% Rx3 – 36.5%

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Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Katz E, et al. Safety and Efficacy of sequential (IV to PO) moxifloxacin vs conventional combination therapies, for the treatment of community-acquired pneumonia in patients requiring initial IV therapy. *J Emerg Med*. 2004;27:395-405.	Trial run from March 2001 to April 2002	Multi-centered, prospective, randomized, open-label study	Moxifloxacin Sequential IV/PO 400 mg QD Comparator IV ceftriaxone 2g QD followed by PO cefuroxime 500 mg bid Comparator treated subjects could also receive IV/PO azithromycin for suspected cases of atypical pneumonia (500 mg IV QD for 2 days followed by 500 mg IV/PO QD for a total of 7 to 10 days for hospitalized subjects or 500 mg IV/PO first dose followed by 250 mg PO QD for 4 days for non-hospitalized subjects) and/or IV/PO metronidazole 500 mg every 6 h for suspected cases of aspiration or anaerobic pneumonia.	Efficacy Total–221 Moxifloxacin–108 Comparator–113 Safety Total–335 Moxifloxacin–167 Comparator–168 Microbiologically Valid Total–50 Moxifloxacin–22 Comparator–28	Adult subjects = 18 years of age who required initial IV therapy with CAP and nursing-home acquired pneumonia including suspected cases of aspiration or anaerobic pneumonia Radiologic evidence of a new or progressive pulmonary infiltrate consistent with pneumonia (based on radiologist's written report confirming the presence of a pneumonic infiltrate) and the presence of at least two characteristic signs or symptoms of pneumonia, including a productive cough with purulent or mucopurulent sputum, tracheobronchial secretions (> 25 polymorphonuclear cells [PMNs]/low-power field [LPF] on Gram stain), or change in the character of sputum (increased volume or purulence); dyspnea or tachypnea (respiratory rate >20 breaths/minute); rigors or chills; pleuritic chest pain; auscultatory findings on pulmonary examination of rales/crackles and/or evidence of pulmonary consolidation; fever (e.g., oral temperature > 38°C/100.4°F or hypothermia (rectal or core temperature < 35°C/95.2°F); and white blood cell (WBC) count = 10,000/µL or = 15% immature neutrophils (bands), regardless of the peripheral WBC count, or leukopenia with a total WBC count < 4500/µL	Effiacy Primary – Clinical response at test-of-cure (TOC) visit Secondary Bacteriological response at TOC Safety All subjects receiving at least one dose of study drug were evaluated for drug safety (intent-to-treat population). Each patient was carefully monitored for adverse events, including abnormal clinical laboratory test results	Efficacy Clinical cure at TOC: Moxifloxacin–83.3% Comparator–79.6% Clinical cure at follow–up: Moxifloxacin–80.2% Comparator–74.7% Microbiological cure at TOC: Moxifloxacin–82.3% Comparator–62.5% Safety Drug–related AEs Moxifloxacin–18.0% Comparator–16.1%

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Lode H, Grossman C, Choudhri S, et al. Sequential IV/PO moxifloxacin treatment of patients with severe community-acquired pneumonia. *Respir Med*. 2003;97:1134-1142.	Not given	One multi-center, prospective, phase III, double-blinded, North American study where patients were randomized to either IV/PO moxifloxacin or IV/PO fluoroquinolone (IV/PO alatrofloxacin/ trovafloxacin or IV/PO levofloxacin) One multi-national, open-label study where patients were randomized to either IV/PO moxifloxacin QD or IV/PO amoxicillin/ clavulanate ± IV/PO clarithromycin	Moxifloxacin IV/PO 400 mg QD Comparator consisting of IV/PO amoxicillin/clavulanate (1200/625 mg t.i.d.) ± IV/PO clarithromycin (500 mg b.i.d.); or IV/PO alatrofloxacin/ trovafloxacin 200 mg QD (later changed to IV/PO levofloxacin 400 mg QD after concerns of hepatotoxicity) In both arms, patients were treated for 7 - 14 days and received IV antibiotic (60-min infusion) for at least 3 days	Safety Total–479 Moxifloxacin–241 Comparator–238 Efficacy Total–376 Moxifloxacin–190 Comparator –186 Microbilogically Valid Total–132 Moxifloxacin–68 Comparator – 64	Inclusion Patients = 18 years old, mild to moderately severe CAP requiring IV therapy clinically documented by: Presence of fever and/or elevated white blood cell count (> 10000 mm^3), new or progressive infiltrate on a chest radiograph, patient had to have at least one sign or symptom of pneumonia Only severe CAP were included in this analysis Exclusion Residence in a nursing home, hospitalization > 48 hours prior to pneumonia onset, bronchial obstruction, post-obstructive pneumonia, pulmonary tuberculosis, prior therapy with systemic antibiotic for > 24 hours prior to enrollment, moderate to severe liver or renal impairment, prolonged QTc interval, using Class IA or III antiarrhythmics, uncorrected hypokalemia, absolute neutrophil count < 1000 cells/mm^3, significant immunosuppression, rapidly fatal underlying disease	Efficacy Clinical efficacy is reported for the test of cure visit for both trials: 5-7 days post-therapy in the multi-national trial 7-30 days post-therapy for the North American trial Assessment included: Resolution of fever, improved cough and respiratory distress, improved leukocytosis, chest radiographs, ability to tolerate oral therapy, no evidence of GI motility or malabsorption. Safety All patients who received at least one dose of moxifloxacin were evaluated for safety. Safety was monitored by clinical observations and by laboratory tests	Sequential IV/p.o. moxifloxacin was as safe and effective as other fluoroquinolones and a β-lactam/macrolide combination for treating hospitalized patients with severe CAP Clinical success rates were 88% (167/190) for moxifloxacin and 83% (155/186) for comparator-treated patients (95% CI = –1.9%, 12.2%) A switch from IV to PO therapy was made at 5 days for 73% of moxifloxacin- vs 60% of comparator-treated patients ($P < 0.01$) Safety Drug–related AEs Moxifloxacin–48% Comparator–45%

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Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Patel T, Pearl J, Williams J, et al. Efficacy and safety of ten day moxifloxacin 400mg once daily in the treatment of patients with community acquired pneumonia. *Resp Med*. 2000;94:97-105.	Enrollment was conducted between December 1996 and May 1998	Prospective, open-label, multi-center, phase III trial	Moxifloxacin 400 mg QD x 10d	Intent to Treat Total-254 Efficacy Valid Total-196	Inclusion Patients ≥ 18 years old, fever and/or elevated WBC and/or leukocytosis, signs or symptoms of pneumonia, new or progressive infiltrate on chest radiograph Exclusion Allergy to fluoroquinolones, pregnancy, lactation, parenteral antibiotics, mechanical ventilatory support, aspiration, hospitalization, significant liver or renal impairment, severe heart failure, impaired host defenses, tendinopathy, concomitant antibiotic therapy, prolonged QTc due to history or meds, previous enrollment in this study, investigational drug use within 30 days of study enrollment, rapidly fatal underlying disease, other resp disease	Efficacy Clinical response and bacteriological response was based on signs and symptoms and the absence of initial pathogen at end of study (0-6 days after last dose) and follow up (14-35 days after last dose) Safety All patients who received the study drug for any length of time were evaluated for drug safety by clinical observation and lab tests. AEs were rated by severity and relationship to study medication.	Efficacy Overall clinical response for efficacy was 92.9% End of therapy was 96.8% Follow-up was 95.8% Safety The most commonly reported AEs were: Nausea 10% Diarrhea 8% Dizziness 6% Rates of drug related rash were low (2%) Photosensitivity was not reported

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Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Petitpretz P, Arvis P, Marel M, et al. Oral moxifloxacin vs high-dosage amoxicillin in the treatment of mild-to-moderate, community-acquired, suspected pneumococcal pneumonia in adults. *Chest. 2001;119(1):* 185-95.	June 1997 – June 1998 (first patient enrolled to last patient completed)	Prospective, multi-national, multi-center, double-blind, comparative study	Moxifloxacin 400mg QD Comparator Amoxicillin 1g tid All patients were treated for 10 days	Efficacy Total -362 Moxifloxacin – 177 Comparator – 185 Safety Total – 408 Moxifloxacin – 200 Comparator - 208	Inclusion Subjects at least 18 years old presenting with fever, radiologic evidence of an infiltrate, cough, purulent sputum, dyspnea/tachypnea, or auscultatory findings Exclusion History of hypersensitivity to quinolones or penicillins, history of tendinopathy, suspected aspiration pneumonia, severe infection requiring parenteral therapy, concomitant systemic antibacterial therapy, AIDS, significant renal impairment, hepatic disease, neutropenia, pregnancy, lactation, congenital or sporadic QTc prolongation, concomitant meds that increase QTc intervals, hospitalization for >48h, systemic treatment for current pneumonia for >24h prior to enrollment	Efficacy Primary – clinical response, 3 to 5 days after completion of treatment (EOT) Saftey All patients who received at least one dose of moxifloxacin were evaluated for safety	Efficacy Clinical Success Rates at EOT: Moxifloxacin – 91.5% Comparator – 89.7% 95% CI (-4.2, 7.8) Safety Moxifloxacin was well tolerated with drug related adverse events being comparable, phototoxicity and QT prolongation was not observed
Torres A, Muir J-F, Corris P, et al. Effectiveness of oral moxifloxacin in standard first-line therapy in community-acquired pneumonia. *Eur Respir J*. 2003;21:135-143.	Not given	Randomized, double-blind, Phase IIIb trial	Moxifloxacin 400mg qd Comparator Three standard treatments: Amoxicillin 1g tid Clarithromycin 500mg bid Both amoxicillin and clarithromycin together All patients received between 5-15 days of treatments	Efficacy Total–446 Moxifloxacin–215 Comparator–231 Safety Total–477 Moxifloxacin–233 Comparator–244	Inclusion Patients aged 18 years or more with CAP fever, elevated white blood cell count (>100000 μL^{-1}, and signs or symptoms of pneumonia; and with new or progressive infiltrate on a chest radiograph. Exclusion Presence of coexisting disease or treatment considered likely to affect study outcome, allergies to drugs in study; pregnancy/lactation, hospitalization for >48h	Efficacy Clinical response at 3–5 days and 7–10 days (TOC) of treatment, and 28-35 days after the end of treatment Safety All patients who received at least one dose of moxifloxacin were evaluated for safety	Efficacy Clinical Success Rates at TOC: Moxifloxacin–93.5% Comparator–93.9% 95% CI (–4.2, 3.3) Clinical Success Rates at Follow–up: Moxifloxacin–95.3% Comparator–93.7% 95% CI (–2.2, 5.2) Safety Moxifloxacin was significantly better tolerated than standard treatment with fewer drug-related adverse events

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Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Acute Bacterial Maxillary Sinusitis

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Baz MN, Jannetti W, Villaneuva C et al. The efficacy and tolerability of moxifloxacin compared to trovafloxacin in the treatment of acute sinusitis. *Today's Ther Trends*. 1999;17:303-319.	Not given	Prospective, multi-center, randomized, double-blind	Moxifloxacin 400 mg PO QD for 10 days, placebo for evening doses days 1-7, and both doses days 8-10 Trovafloxacin 200 mg PO QD for 10 days	Safety Total–590 Moxifloxacin–288 Trovalfoxacin–302 Efficacy Total–513 Moxifloxacin–253 Trovalfoxacin–260	Inclusion Outpatient men and women at least 18 years of age Diagnosis of acute bacterial sinusitis defined as presence of clinical signs and symptoms = 7 days but = 28 days in duration with radiologic paranasal x-ray confirming maxillary sinusitis At least 2 of the following: nasal congestion, post-nasal discharge, frequent coughing or throat clearing, frontal headache, malar tenderness/pain	Efficacy Clinical response and follow-up sinus x-ray at test-of-cure visit (7-21 days post-treatment) Safety Clinical adverse events, blood chemistry, hematology, and urinalysis	Efficacy 7-21 days post-therapy: Moxifloxacin–88.1% Comparator–89.2% Safety Trovafloxacin patients reported a statistically and clinically significant 4-fold greater incidence of dizziness (20%) than moxifloxacin recipients (5%, $P < 0.001$) A significantly higher proportion of moxifloxacin-treated patients completed the full treatment regimen
Burke T, Villanueva C, Mariano H, et al. Comparison of moxifloxacin and cefuroxime axetil in the treatment of acute maxillary sinusitis. *Clin Ther*. 1999;21(10):1664-1677.	February 16, 1998, to August 25, 1998 (1st patient's 1st visit to last patient's last visit)	Prospective, randomized, multi-center, double-blind, phase III	Moxifloxacin 400 mg PO QD for 10 days, matching placebo 10 days. Cefuroxime axetil 250 mg PO b.i.d. 10 days	Efficacy Total–457 Moxifloxacin–223 Cefuroxime axetil–234 Safety Total–537 Moxifloxacin–263 Cefuroxime axetil–274	Inclusion Outpatient men and women 18 years or older Documented or suspected ABMS (duration > 7 days but $\leq$ 28 days), evidenced by clin. signs and symptoms of acute infection and pos. x-ray (Water's view), symptoms incl. nasal congestion, postnasal discharge, purulent nasal drainage, frequent coughing or throat clearing, frontal headache, and malar tenderness or pain Pos. radiographic criteria incl. at least 1 of following: air fluid level, opacification, or mucosal thickening > 6 mm Females of childbearing age using reliable contraception during exposure to study drug	Efficacy Primary – Clinical response at TOC (7-14 days post-treatment) Secondary – Clinical response at follow-up (27-31 days post-treatment) Safety On basis of physical exam findings, adverse events, electrocardiograms, intercurrent illness, and laboratory tests	Efficacy At EOT: Moxifloxacin–90% Comparator–89% At Follow-up: Moxifloxacin–98% Comparator–98% Safety Drug-related AEs Moxifloxacin–37% Comparator–26%

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Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Acute Bacterial Maxillary Sinusitis

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Data on File. Schering-Plough Corporation. Kenilworth, New Jersey.	April 2000 to March 2002	A retrospective, claims databse study	AS episodes were included in the study analysis, only where either moxifloxacin or levofloxacin were identified as the initial therapy	Moxifloxacin – 3,358 Levofloxacin – 1,522	Treatment episodes were selected from the database by first identifying all office or hospital outpatient visits with an ICD-9 diagnosis of acute sinusitis (AS). For each visit, the date of the diagnosis of acute sinusitis was determined to be the episode index date. The database was then searched for all episodes in which moxifloxacin or levofloxacin were prescribed within five days from the episode index date. The date of the prescription for either moxifloxacin or levofloxacin was defined as the drug index date. Inclusion and exclusion criteria were established *a priori* and applied to the treatment episodes that were used in the analyses to maximize the likelihood that the drug was being prescribed to treat acute sinusitis. The treatment episodes were monitored for a 30 day period following the drug index date, or in the case of treatment failure, for 30 days after the second antibiotic prescription was filled and continued until no treatment failure was observed.	Enpoints measure in this study included total therapy duration and monotherapy duration, treatment failure, recurrence of infection, and treatment costs.	• The average duration of therapy was 10.4 days in the moxifloxacin group versus 12.4 days in the levofloxacin group (p <0.001). • Moxifloxacin treated patients had a 36% lower probability of recurrence than levofloxacin treated patients (p=0.0062). • The observed failure rate was also significantly lower in the moxifloxacin group compared to the levofloxacin group (10.4% versus 14%, respectively, p = 0.003). • Cost analysis also demonstrated that the average total treatment charges ($171 moxifloxacin verses $211 levofloxacin, p = 0.03) and average pharmacy charges ($103 moxifloxacin versus $117 levofloxacin, p <0.0001) were significantly lower in the moxifloxacin-initiated group. • Ordinary least squares analysis demonstrated that the duration of the original prescription was 1.65 days shorter for the moxifloxacin group compared to the levofloxacin group. • The duration of therapy, both monotherapy and duration of all antibiotics, was significantly shorter in the moxifloxacin treated group when compared to the levofloxacin group (2.06 and 1.97 days, respectively, p<0.0001).

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Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Acute Bacterial Maxillary Sinusitis

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Gehanno P, Berche P, Perrin A. Moxifloxacin in the treatment of acute maxillary sinusitis after first-line treatment failure and acute sinusitis with high risk of complications. *J Int Med Res*. 2003;31:435-448.	Not given	Prospective, multicenter study after first-line treatment failure (group 1), and acute sinusitis with high risk of complications (group 2)	Moxifloxacin All patients were treated with 400 mg PO QD for 7 days	Intent to Treat 255 Per Protocol 216 Total 258	Inclusion Eligible patients were men and women = 18 years of age, with suspected acute bacterial sinusitis and evidence of purulent rhinorrhoea confirmed by nasal endoscopy Exclusion Suspected bacteremia or meningitis; history of sinus surgery; chronic sinusitis; > 2 episodes of sinusitis within the past 6 months; immunosuppression (neutropenia, documented HIV infection); need for concomitant systemic antimicrobial therapy; pregnancy or breast-feeding; documented hypersensitivity to moxifloxacin, its excipients, or other quinolones; renal impairment (baseline serum creatinine > 265 µmol/L); severe hepatic impairment or increased transaminase rate (×5 the upper limit of normal); congenital or acquired prolonged QT intervals; hydroelectrolytic disorders; uncorrected hypokalemia; clinically significant bradycardia, especially cardiac insufficiency through reduction of the left ventricular ejection fraction; previous history of clinically significant arrhythmia; and/or co-administration of other medications reported to prolong QT intervals	Efficacy Clinical responses were recorded on days 3-4 of treatment (V2), days 7-10 post-treatment Safety Safety monitored by clinical observations and lab tests of renal, hepatic, and hematological function. Adverse events subjectively rated by investigator as to severity and the relationship to study	Efficacy The clinical success rate 7-10 days posttreatment was 92.6% in the PP population. Bacteriological success rates were 95.7% after 3-4 days of treatment, and 97.2% and 95.2%, in group 1 and group 2, respectively, at 7-10 days post-treatment Overall, moxifloxacin therapy resulted in rapid bacteriological eradication, with a high rate of clinical success Safety Drug-related adverse events, including abdominal pain (2.4%), nausea (2.4%), and diarrhea (1.2%), were reported in 12.2% of patients

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Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Acute Bacterial Maxillary Sinusitis

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Klossek JM, Siegert R, Nikolaidis P, Arvis P, et al. Comparison of the efficacy and safety of moxifloxacin and trovafloxacin for the treatment of acute, bacterial maxillary sinusitis in adults. *The Journal of Laryngology & Otology*. 2003;117:43-51.	November 1998 to June 1999	Prospective, multi-national, multi-center, randomized, double-blind, comparative study	Moxifloxain 400 mg PO QD for 7 days Trovafloxacin 200 mg PO QD for 10 days	Efficacy Total-452 Moxifloxacin -223 Trovafloxacin -229 Safety Total-499 Moxifloxacin -248 Trovalfoxacin -251	Inclusion Outpatients men and female ≥ 18 years old with acute sinusitis based on six typical signs and symptoms, and radiographic evidence Exclusion History of hypersensitivity to quinolones, congenital or sporadic syndromes of QT prolongation, concomitant meds that can prolong the QT interval, suspected meningitis, past sinus surgery, chronic sinusitis, recurrence of ≥ 2 episodes of acute sinusitis within the past 6 mo, concomitant use of systemic antibiotic, pregnancy, lactat ion, history of seizures, convulsive disorders, major renal impairment, ALT/bilirubin > 3xULN, previous enrollment in the study	Efficacy Clinical response determined at the during study (3-5 d), post therapy (7-10 d), and follow up (3-4 wks after end of treatment) Primary-Clinical resolution at post therapy Safety Evaluations performed between first dose and final follow up visit, incidence and severity of AE was noted for relationship to drug	Efficacy Moxifloxacin vs trovafloxacin: 96.9% vs 92.1% (95% CI=0.6%; 8.9%) Safety The two most commonly reported drug related AEs was associated with the CNS and digestive system, GI events were similar in both treatment groups CNS events were reported 5x more often in trovafloxacin (11.6%) vs moxifloxacin (2%)
Rakkar S, Roberts K, Towe BF, Flores SM, Heyd A, Warner J. Moxifloxacin versus amoxycillin clavulanate in the treatment of acute maxillary sinusitis: a primary care experience. *Int J Clin Pract.* 2001;55(5):309-315.	Not given	Prospective, multi-center, randomized, non-blinded, phase III 2-arm, comparative study	Moxifloxacin 400 mg PO QD for 10 days Amoxycillin clavulanate 875 mg PO bid for 10 days	Efficacy Total–341 Moxifloxacin–170 Amoxicillin/ Clavulanate–171 Safety Total–471 Moxifloxacin–234 Amoxicillin/ Clavulanate–237	Inclusion Outpatient men and non-pregnant women ≥18 years old with a clinical diagnosis of acute suspected bacterial sinusitis (i.e., ≥7d and ≥30d duration) wirh clinical signs and symptoms of sinusitis	Efficacy Primary-Clinical resolution at the test-of-cure visit (14-21 days post-treatment) Secondary-Clinical relapse at follow-up (day 26-46 post-therapy visit) Safety Safety monitored by clinical observations and lab tests of renal, hepatic, and hematological function. Adverse events subjectively rated by investigator as to severity and the relationship to study	Efficacy For ITT population moxifloxacin was statistically equivalent to amoxicillin/clavulanate at TOC visit, 85% vs 82%; 95% CI = (-6%, 13%). Analysis of PP pop. confirmed statistical equivalence, 86% vs 84%; 95% CI = (-7%, 13%). Safety Of the 471 patients who were evaluated for safety, treatment emergent adverse events were reported for 136 (58%) moxi and 124 (52%) amox/clav treated patients.

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Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Acute Bacterial Maxillary Sinusitis

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Siegert R, Gehanno P, Nikolaidis P, et al. A comparison of the safety and efficacy of moxifloxacin (BAY 12-8039) and cefuroxime axetil in the treatment of acute bacterial sinusitis in adults. *Respir Med*. 2000;94:337-344.	November 21, 1996, to June 25, 1997 (1st patient's 1st visit to last patient's last visit)	Prospective, 2 armed, randomized, multi-center, double-blind, parallel-group, active controlled	Rx1: moxifloxacin 400 mg PO QD for 7 days, placebo for evening doses days 1-7, and both doses days 8-10 Rx2: cefuroxime axetil 250 mg b.i.d. for 10 days	Efficacy Total–436 Moxifloxacin–211 Cefuroxime axetil–225 Safety Total–493 Moxifloxacin–242 Cefuroxime axetil–251	Inclusion Outpatient men and women at least 18 years of age Suffering from acute bacterial sinusitis either bacteriologically documented or clinically suspected using radiological paranasal sinus x-ray At least 2 of the following: nasal congestion, post-nasal drainage, frequent coughing or throat clearing, frontal headache, malar tenderness/pain, purulent nasal drainage	Efficacy Primary – Clinical response at end-of-therapy (EOT), defined as day 14 assessment, i.e., 3 days post-end of therapy Secondary – Clinical response during therapy (days 7-9) and follow-up (days 27-31 after treatment) Secondary – Bacteriological response at EOT (day 14) Safety Clinical adverse events, blood chemistry, hematology, and urinalysis	Efficacy For PP pop. the clinical success rate at EOT in the moxifloxacin group was sig. higher (96.7%) than the cefuroxime axetil group (90.7%; CI = 1.5%, 10.6%) At follow-up 21-28 days after EOT, 90.7% of moxifloxacin group and 89.2% of cefuroxime axetil group still assessed as successes; number of relapses and patients lost to follow-up were similar in each group; 95% CI = -4.3%, 5.4% indicates no sig. difference between treatments Safety Treatment emergent adverse events were reported in 134 (47%) of moxi treated patients and 162 (54%) of trov treated patients
Gehanno P, Darantiere S, Dubreuil C, et al. A prospective, multicentre study of moxifloxacin concentrations in the sinus mucosa tissue of patients undergoing elective surgery of the sinus. *J Antimicrob Chemother*. 2002;49:821-826.	Not given	Multi-center, controlled, open-label, 7 non-parallel groups, and one control group	Moxifloxacin 400 mg PO QD for 5 days Group A, last drug intake 2 h before surgery; group B, 3 h before surgery; group C, 4 h before surgery; group D, 6 h before surgery; group E, 12 h before surgery; group F, 24 h before surgery; group G, 36 h before surgery	Per Protocol 42 in moxifloxacin group, 6 in control group	Exclusion Outpatient men and women =18 years of age Hypersensitivity to quinolones; pregnancy and lactation; recent participation in another clinical trial; liver enzyme abnormalities; raised creatinine; positive test for HIV, hepatitis C or B; any laboratory test result that could contraindicate sinus surgery	Efficacy Concentration of moxifloxacin in sinus tissues and in plasma at sampling time Safety Clinical adverse events	The geometric mean moxifloxacin plasma concentration increased from 2.32 mg/L at 2 h to a maximum of 3.37 mg/L at 4 h post-dose, decreasing to 0.37 mg/L at 36 h post-dose The moxifloxacin concentration in sinus mucosa was consistently greater than that in plasma, being 4.56-5.73 mg/kg from 2 to 6 h and 2.81-1.25 mg/kg from 12 to 36 h post-dose. The elimination rates in plasma and sinus tissues were similar. The tissue/plasma ratio was ≈200% between 2 and 6 h, and up to 328.9% at 36 h Tissue levels exceeded the MIC_{90} of all pathogens commonly causing acute sinusitis (e.g., 5-30 × MIC for *Streptococcus pneumoniae*: 0.25 mg/L)

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Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Acute Exacerbations of Chronic Bronchitis

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Chodosh S, DeAbate CA, Haverstock D, et al. Short-course moxifloxacin therapy for treatment of acute bacterial exacerbations of chronic bronchitis. *Respir Med.* 2000;94:18-27.	November 21 1996, to April 7 1998 (1st patient's 1st visit to last patient's last visit)	Prospective, randomized, double-blind, parallel	Rx1: moxifloxacin 400 mg PO QD 5 days Rx2: moxifloxacin 400 mg PO QD x 10 days Rx3: clarithromycin 500 mg PO b.i.d. x 10 days Rx1 and Rx2 included placebo for uniform dosing	Efficacy Total–420 Rx1–143 Rx2–148 Rx3–129 Safety Total–926 Rx1–312 Rx2–302 Rx3–312	Inclusion Men or women 18 years or older With acute bacterial exacerbations of chronic bronchitis Increased purulent/mucopurulent sputum and at least 1 of following: increased cough, dyspnea, or sputum volume or the presence of fever (oral temperature > 100.4°F) at time of screening	Efficacy Primary – Clinical response and bacteriological response at end of therapy (post-therapy days 0-6) and at follow-up (post-therapy days 7-17) Safety Physical exam findings, ECGs, adverse events, intercurrent illness, and lab tests	Efficacy Overall clinical resolution was 89% for 5d moxi-floxacin vs. 91% for 10d moxifloxacin vs. 91% for 10d clarithromycin. Bact. eradication rates at end of therapy were 94% and 95% for 5d and 10 d moxifloxacin, respectively; and 91% clarithromycin. Eradication rates at follow-up were 89% for 5d and 91% for 10d moxifloxacin and 85% for clarithromycin. Safety Drug related events were reported for 26%, 30% and 35% in 5d moxifloxacin, 10d moxifloxacin and clarithromycin groups, respectively

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Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
DeAbate CA, Mathew CP, Warner JH, et al. The safety and efficacy of short course (5-day) moxifloxacin vs azithromycin in the treatment of patients with acute exacerbation of chronic bronchitis. *Respiratory Medicine*;94:1029-1037.	Not given	Prospective, double-blind, randomized, multi-center trial	Moxifloxacin 400 mg PO QD for 5 days Azithromycin 500 mg PO QD for the first day followed by 250 mg QD for 4 days	Efficacy Total-464 Moxifloxacin - 221 Azithromycin - 243 Safety Total-567 Moxifloxacin - 283 Azithromycin - 284	Inclusion Outpatients $\geq$ 18 years old, suspected ABECB, COPD patients were eligible, all required to have increased purulent/mucopurulent sputum and one or more of the following: increased cough, increased dyspnea, increased sputum volume, fever) Exclusion Allergy/severe adverse reactions to carboxyquinolone derivatives or azalide/macrolide derivatives, fluoroquinolone related tendinopathy, n.p.o., pregnant, lactating, chest x ray suggestive of new pneumonia, recent diagnosis/unresolved lung or chest cavity malignancy, neutrophil > 1000mm^{-3}, CD4 > 200mm^{3}, significant immunosuppression, significant liver impairment, dialysis, history of prolonged QTc, concomitant or systemic (24 h prior to enrollment) antibacterial use, use of drugs that affect QTc,	Efficacy Determined at end of therapy (0-6 d post tx) and test of cure (14-21 d post tx) Based on auscultatory findings, fever, presence of WBC > 12000 cells/mm, prolonged expiratory phase, chest pain, cough frequency and severity, sputum characterics Bacteriologic Response Evaluation performed during therapy (1-5 d), end of therapy visit (0-6 d post tx), and test of cure visit (14-21 d post tx) Safety Patients that received at least one dose were evaluated for safety by physical exams, ECGs, AEs, and lab tests.	Efficacy End of therapy: Moxifloxacin -91% Azithromycin -92% Test of cure: Moxifloxacin -88% Azithromycin -88% Bacteriologic Response End of therapy: Moxifloxacin -96% Azithromycin -94% Safety Drug related AE: Moxifloxacin -22% Azithromycin -17% The two most common events were diarrhea and nausea and were similar in both groups.

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Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Acute Exacerbations of Chronic Bronchitis

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Grassi C, Casali L, Tellarini M, et al. Efficacy and safety of short course (5 day) moxifloxacin vs 7 day ceftriaxone in the treatment of acute exacerbations of chronic bronchitis. *Journal of Chemotherapy.* 2002;14(6):597-608.	Not given	Multicenter, open, randomized, parallel group, phase IV study	Moxifloxacin 400 mg PO QD x 5 days Ceftriaxone 1g IM QD for 7 days	Efficacy Total - 423 Avelox – 213 Ceftriaxone - 210 Safety Total - 470 Avelox - 240; Ceftriaxone - 230 Bacteriologically valid Total - 66 Avelox - 36 Ceftriaxone - 30	Inclusion Outpatients and patients hospitalized ≤ 48 hrs, ≥ 18 years old with ABECB, class I and II Anthonisen were eligible, chest radiograph to confirm absence of pulmonary abnormalities Exclusion Pretreatment with systemic antibacterial within 3 days of enrollment, class IV NYHA classification, severe resp. tract infection requiring mechanical ventilation, pneumonia, active pulm. TB, cystic fibrosis, severe bronchiectasis, severe liver impairment, HIV infection, renal dialysis, neutropenia, any disease expected to reduce life expectancy to ≤ 6 mo, use of other investigational agents within 30 days of starting study treatment, pregnancy, lactation, inadequate contraception, congenital or sporadic syndromes of QTc prolongation, meds that affect the QTc interval	Primary-clinical response at test of cure (10 d after end of tx) Secondary-bacteriological response at test of cure, clinical response at end of treatment (1-2 d after end of tx), clinical response at test of cure, change in symptoms of infection, number of exacerbations during the 6 mo follow-up, time to relapse in clinically cured patients during follow-up	Efficacy Clinical response at TOC: Moxifloxacin - 91% Ceftriaxone – 89% Bacteriological response at TOC: Moxifloxacin - 92% Ceftriaxone – 93% Safety During therapy, adverse events considered possiblely or probablely related to the study occurred in 5% (n=12) Avelox and 0.4% (n=1) in Ceftriaxone recipients. Most AEs were mild to moderate and involved the GI system in both tx.
Hautamaki D, Bruya T, Kureishi A, Warner J, Church D. Short-course (5-day) moxifloxacin versus 7-day levofloxacin therapy for treatment of acute exacerbations of chronic bronchitis. *Today's Ther Trends.* 2001;19:117-136.	Not given	Prospective, randomized, double-blind	Moxifloxacin 400 mg PO QD for 5 days (short course) Levofloxacin 500 mg PO QD for 7 days	Efficacy Total–461 Moxifloxacin–227 Levofloxacin–234 Safety Total–594 Moxifloxacin–296 Levofloxacin–298	Inclusion Men and women 18 years or older with underlying chronic bronchitis defined by daily production of sputum on most days for ≥ 3 consecutive months for > 2 consecutive years and an ABECB of < 30 days duration Must have had increased purulent/mucopurulent sputum (e.g., opaque, yellow-green, viscous material) and at least 1 of the following: increased cough, increased dyspnea, increased sputum volume, or presence of fever (oral temp > 38°C)	Efficacy Primary – Clinical response at test of cure (7-21 days) and follow-up (27-38 days) Secondary – Bacteriological response at post-therapy (7-21 days) and follow-up (27-38 days) Safety Physical examination, adverse event, intercurrent illness and laboratory tests (hematology, blood chemistry and urinalysis tests)	Efficacy For PP pop. clinical resolution at TOC visit (7-21 days post-treatment) was 93% for moxifloxacin vs. 94% for levofloxacin (95% CI= -6.2%, 2.8%) For ITT pop. clinical resolution at TOC visit were similar, 92% moxifloxacin and 95% levofloxacin,(CI not given) Bacteriological eradication rates for the microbiologically-valid group at TOC were 96% for both treatment groups. Safety Drug-related AEs were 24% for moxifloxacin and 25% for levofloxacin

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Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Acute Exacerbations of Chronic Bronchitis

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Kreis SR, Herrera N, Golzar N, et al. A comparison of moxifloxacin and azithromycin in the treatment of acute exacerbation of chronic bronchitis. *J Clin Outcomes Manage*. 2000;7(12):33-37.	September 1999 to May 2000	Prospective, multi-center, non-blinded, phase IIIb	Moxifloxacin 400 mg PO QD for 5 days (short course) Azithromycin PO 500 mg day 1, 250 mg PO QD for 4 days	Efficacy Total–355 Moxifloxacin–179 Azithromycin–176 Safety Total–399 Moxifloxacin–201 Azithromycin–198 Number of responses for patient-reported outcomes was less than ITT population	Inclusion Male or non-pregnant female outpatients 18 years or older with clinically documented ABECB of suspected bacterial origin and without a recent chest x-ray suggestive of a new pneumonia or lobar consolidation Underlying chronic bronchitis defined by daily production of sputum on most days for $\geq$ 3 consecutive months for > 2 consecutive years Symptoms of increased sputum purulence and at least 1 of the following: increased sputum volume, increased cough, or increased dyspnea or fever (> 38°C orally)	Efficacy Clinical response at test of cure (14-21 days post-therapy) Patient-reported outcomes from a series of five questions Safety Assessed on the basis of investigator-determined, drug-related adverse events	Efficacy Clinical resolution at follow-up visit (14-21 days) was 85% for moxifloxacin and 81% for azithromycin patients (95% CI = -6.0%, 14.0%) More moxifloxacin patients (40%) reported symptomatic relief by day 3 than did azithromycin patients (27%) (p=0.012). More moxifloxacin patients (36%) reported a return to normal activities within 3 days of therapy than did azithromycin patients (26%) Safety Drug related adverse events: Moxifloxacin – 12% Azithromycin – 9%
Miravitlles M, Roz F, Cobos A, Kubin R, Tillotson G. The efficacy of moxifloxacin in acute exacerbations of chronic bronchitis: a Spanish physician and patient experience. *Int J Clin Pract.* 2001;55:437-441.	Not given	Open, community based	Moxifloxacin 400 mg PO QD for 5 days	5737 patients enrolled, 5221 valid for efficacy	Inclusion Outpatients 18 years or older with acute bacterial exacerbation of bronchitis 2 or 3 of the following presenting signs: increased sputum volume, increased sputum purulence, and increased dyspnea, in addition to productive cough	Efficacy Clinical response at 7 days and 45 days after the start of therapy Safety Clinical adverse events	Efficacy Clinical response (cure and/or improvement) after 7 days was reported as 93%. Long-term cure rate was 97.3% (CI=94.4-96%) Safety Adverse events were reported in 3.5% of patients with the most commonly reported events being diarrhea, nausea and dizziness, and epigastric pain.

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Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Acute Exacerbations of Chronic Bronchitis

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Miravitlles M, Zalacain R, Murio C, et al. Speed of recovery from acute exacerbations of chronic obstructive pulmonary disease after treatment with antimicrobials: results of a two-year study. *Clin Drug Invest.* 2003;23:439-450.	Not given	Multi-center, observational	*Year 1:* The antimicrobial prescribed for the 1st exacerbation was maintained for all further exacerbations in year 1; choice of antimicrobial could be changed at the baseline visit for year 2 *Year 2:* Moxifloxacin 400 mg QD for 5 days was given to 50% of patients with ABECB	Total–614 Moxifloxacin–111 Amoxicillin/clavulanate–171 Cefuroxime–83 Clarithromycin–80 Azithromycin–37 Other–132	Inclusion Men or women 18 years or older Clinically stable respiratory disease in the previous month A smoking history of at least 10 pack-years	Efficacy Time to recovery after treatment Clinical response was evaluated at 6-month intervals during the 2-year period; 1 year after inclusion, patients attended the 3rd visit, the baseline visit for the period when moxifloxacin was added to the treatment options	Mean time to recovery overall was 4.6 ± 3.3 days with moxifloxacin and 5.8 ± 4.6 days with comparators ($p<0.01$) 27 patients treated with moxiflxoacin in year 2 recovered ina mean of 3.7 ± 3.1 days, with the same patients treated with comparators in year 1 recovered in 6.8 ± 4.6 days ($p=0.02$). 66 patients treated with comparators in both years, mean time to recovery was 7.4 ± 7.3 days in year 1 and 5.5 ± 3.5 days in year 2 ($p=0.24$). Moxifloxacin treatment produced a statistically significant reduction of 18% - 25% in the time to recovery compared with other antibiotics. Treatment compliance was significantly betterh with moxiflxoacin than with comparator.

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Miravitlles M, Llor C, Naberan K et al. Effect of various antimicrobial regimens on the clinical course of exacerbations of chronic bronchitis and chronic obstructive pulmonary disease in primary care. *Clin Drug Invest.* 2004;24:63-72.	February 2001 and May 2002	Observational, non-randomized, open-label study	Moxifloxacin 400 mg QD for 5 days Amoxicillin/clavulanic acid (co-amoxiclav) 500 mg/125 mg tid x 10 days Clarithromycin 500 mg bid x 10 days	Moxifloxacin-575 Co-amoxiclav-460 Clarithromycin-421	Inclusion A productive cough for at least 3 months per year for 2 consecutive years For a diagnosis of COPD, the observation of a non-reversible airflow obstruction was required, characterized on forced spirometry by a forced volume in 1 second (FEV_1) < 80% of the theoretical value and an FEV_1/forced vital capacity (FVC) ratio of < 70% in a stable phase Diagnosis of an exacerbation was defined by the patient's symptoms, increase in the usual level of dyspnea, increase in sputum volume, and/or increase in sputum purulence	Efficacy The investigator evaluated the course of the exacerbation as a function of the resolution of the symptoms The treatment was considered to have been successful if cure or clinical improvement was achieved Cure was defined as the complete resolution of the 3 cardinal symptoms of exacerbation Safety Clinical adverse events	Efficacy Clinical cure rate:remission of the 3 cardinal symptoms of exacerbation (increased expectoration, change in sputum purulence, and increased dyspnea) were similar on the 10th day: 67% in the group receiving moxifloxacin, 65% in those taking co-amoxiclav, and 64% in those taking clarithromycin (P = 0.38) Differences in the clinical cure rates were observed on day 3 (moxifloxacin 20%, co-amoxiclav 9.6%, and clarithromycin 6.5%) and day 5 (moxifloxacin 49%, co-amoxiclav 26.5%, and clarithromycin 30%). Cure rates were significantly higher in the moxifloxacin group vs the other 2 treatment groups (P < 0.001 for both days) The time to resolution of symptoms was shorter in the moxifloxacin group vs the other 2 groups.

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Schaberg T, Ballin I, Huchon G, et al. A multinational, multicentre, non-blinded, randomized study of moxifloxacin oral tablets compared with co-amoxiclav oral tablets in the treatment of acute exacerbation of chronic bronchitis. *The Journal of International Medical Research.* 2001;29:314-328.	December 1, 1998 to June 9, 1999	Multi-national, multi-centre, non-blinded, randomized trial	Moxifloxacin-400 mg PO QD x 5 days Co-amoxiclav-625 mg PO tid x 7 days	Efficacy Total-512 Moxifloxacin-261 Co-amoxiclav-251 Safety Total-575 Moxifloxacin-292 Co-amoxiclav-283	Inclusion Male and female patients ≥ 18 years old with chronic bronchitis, clinical symptoms of ABECB of Anthonisen type I and II, increasing dyspnea, and/or increasing sputum volume Exclusion Hypersensitivity to study drug or related compounds, pregnancy, lactation, female patients using inadequate contraception, significant liver impairment, renal insufficiency, congenital or sporadic syndromes of QTc prolongation, concomitant meds that increase the QTc interval, history of quinolone related tendinopathy, concomitant systemic antibacterial agent or use of antibacterial agent within 48 hours of screening, participating in any clinical trial within 2 mo of screening	Efficacy Primary: clinical response at 14 days Secondary: clinical responses at follow-up (28-35 days post tx), bacterial responses at 14 days and follow-up Safety All AE severity and relation to trial drug was assessed, AEs occurring 7 days and serious AEs occurring up to 30 days after stopping meds were reported Safety analysis was performed on all patients who received at least 1 dose of study meds	Efficacy Clinical response at 14 days: Moxifloxacin-96.2% Co-amoxiclav-91.6% (95% CI: 0.4%;8.7%) At follow-up: Moxifloxacin-89.4% Co-amoxiclav-87.5% (95% CI: -3.5%;7.5%) Bacterial response at 14 days (ITT pop): Moxifloxacin-78.2% Co-amoxiclav-80.5% Bacterial response at follow-up (ITT pop): Moxifloxacin-83.8% Co-amoxiclav-79% Safety Dizziness and nausea were more frequent with moxifloxacin Diarrhea and headache were more frequent with co-amoxiclav

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Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Acute Exacerbations of Chronic Bronchitis

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Wilson R, Kubin R, Ballin I, et al. Five day moxifloxacin therapy compared with 7 day clarithromycin therapy for the treatment of acute exacerbations of chronic bronchitis. *J Antimicrob Chemother*. 1999;44(4):501-513.	November 22, 1996, to June 8, 1997 (1st patient's 1st visit to last patient's last visit)	Prospective, multi-national, multi-center, double-blind, randomized, 2 armed, controlled	Moxifloxacin 400 mg PO QD x 5 days, matching placebo, including days 6 and 7 Clarithromycin 500 mg PO b.i.d. x 7 days	Safety Total–745 Moxifloxacin–374 Clarithromycin – 371 Efficacy Total–649 Moxifloxacin–322 Clarithromycin – 327 Microbiologically valid: Total - 229 Moxifloxacin -115 Clarithromycin - 114	Inclusion Adults with moderate to severe ABECB including: Patients suffering from chronic bronchitis as defined by World Health Org. criteria At least 2 of following: ABECB symptoms: purulent/mucopurulent sputum, increasing sputum volume, increasing dyspnea (Anthonisen type I or II exacerbation) Exclusion Known antibiotic allergy, pregnancy or lactation, significant renal or hepatic impairment, concomitant serious illness, recent antibiotic therapy, or recent participation in another clinical trial	Efficacy Primary – Clinical response at day 14 Secondary –Clinical response at end of therapy (EOT) (day 7) and at follow-up (dasy 28-35) Clinical response at EOT (day 7), day 14, and at follow-up (days 28-35) in patients w/bact.-proven ABECB at start of study Bact. response at EOT (day 7), day 14, and follow-up (days 28-35) Safety Clinical adverse events, serum biochemistry, hematology, and urinalysis	Efficacy Clinical success rate day 14: Moxifloxacin–89.1% Comparator–88.4% Bacteriological success rate day 14: Moxifloxacin–77.4% Comparator–62.3% Safety Drug related adverse events: Moxifloxacin – 21.4% Clarithromycin – 22.1% Nausea and diarrhea were the most common adverse events for both treatments.
Wilson R, Allegra L, Huchon G, et al. Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute Exacerbations of chronic bronchitis. *Chest*. 2004;125:953-964.	Not given	Randomized, double-blind study of 2 parallel treatment arms	Moxifloxacin 400 mg QD 5 days Comparator amoxicillin 500 mg t.i.d. 7 days, OR clarithromycin 500 mg b.i.d. 7 days, OR cefuroxime axetil 250 mg b.i.d. 7 days	Per Protocol Moxifloxacin -274 Comparator-298 Total-572 Intent to Treat Moxifloxacin -354 Comparator-298 Total-572	Inclusion Outpatients aged $\geq$ 45 years with documented chronic bronchitis (CB) were eligible for enrollment during an ABECB-free period if they had: A history of cigarette smoking of at least 20 packs/year, two or more documented ABECB in the previous year, or $FEV_1 < 85\%$ of predicted value at enrollment visit (FEV_1: forced expiratory volume in the first second Exclusion Previous adverse reaction to study drugs, pregnancy or lactation, syndrome of QTc prolongation, severe renal or hepatic impairment, or lung disease other than CB that could affect the clinical evaluation of study medication	Efficacy Primary – Clinical response 7-10 days post-therapy Other – Further antimicrobial use, time to next ABECB Bacteriological success Safety Clinical adverse events	Efficacy Intent to treat population the clinical success was 87.6% vs 83% for the comparator (95% CI=0.7, 9.5) In per protocol clinical success was 87.2% vs 84.2% for the comparator (95% CI=-.3, 8.5)

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Uncomplicated Skin and Skin Structure Infections

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Del Rosal P, Fabian G, Vick-Fragoso R, et al. Efficacy and safety of moxifloxacin vs cephalexin (with or without metronidazole) in the treatment of mild to moderate uncomplicated skin and skin structures infections (uSSSI). Poster presented at: Interscience Conference on Antimicrobial Agents and Chemotherapy; September 26-29, 1999; San Francisco, Calif.	April 26, 1997 (1st patient's 1st visit), to May 15, 1998	Multi-centre, multi-national, prospective, parallel group, randomized, controlled, double blind	Rx1: moxifloxacin 400 mg PO QD for 5-14 days Rx2: cephalexin 500 mg t.i.d. with or without metronidazole 400 mg t.i.d. for 5-14 days	Efficacy Total–385 Rx1–191 Rx2–194 Safety Total–451 Rx1–227 Rx2–224	Inclusion Patients 18 years and above with mild to moderate uncomplicated skin and soft tissue infection One or more of following symptoms within 24 hours before enrollment in the st udy: fever > 38°C or chills, edema of skin/soft tissues, erythema of skin/soft tissues, purulent exudate, local pain or tenderness, local hyperthermia	Efficacy Primary – Clinical response at 1-7 days after end of therapy (EOT) (at visit 4) Secondary – Clinical and bacteriological responses on days 3-6 of therapy (at visit 2), 2-3 days later (at visit 3) and 8-21 days after EOT (at visit 5), also bacteriological response assessed 1-7 days after EOT (at visit 4) Safety Clinical adverse events, blood chemist ry, hematology, urine sediment, urinalysis, and 12-lead ECG	Efficacy Clinical success rate at EOT: Rx1–92.7% Rx2–92.8% Clinical success rate at follow–up: Rx1–99.4% Rx2–98.2% Overall clinical success rate: Rx1–91.8% Rx2–91.0% Bacteriological response at EOT: Rx1–89.0% Rx2–93.8% Safety Drug related adverse events: Rx1–35.7% Rx2–25.9%
Parish LC, Routh HB, Miskin B, et al. Moxifloxacin versus cephalexin in the treatment of uncomplicated skin infections. *Int J Clin Pract.* 2000;54(8):497-503.	August 20, 1997, to May 5, 1998 (1st patient's 1st visit to last patient's last visit)	Prospective, comparative, controlled, randomized, multi-center, double-blind	Rx1: moxifloxacin 400 mg PO QD x 7 days Rx2: cephalexin 500 mg PO t.i.d. x 7 days	Efficacy Total–351 Rx1–180 Rx2–171 Safety Total–399 Rx1–201 Rx2–198	Inclusion Male and female outpatients aged 18 years or older with acute uncomplicated skin and superficial skin structure or wound infections Two or more of following symptoms within 24 hours before enrollment: fever > 38°C, skin/soft tissue edema, erythema of skin/soft tissues, purulent exudate, local pain, or local warmth	Efficacy Primary – Clinical response 7-21 days post-therapy Secondary – Clinical and bacteriological response during therapy (days 3-4), as well as bacteriological response 7-21 days post-therapy Safety Physical examination findings, reported clinical adverse events, intercurrent illness, ECG, concomitant medication use, and lab tests results including hematology, blood chemistry, urinalysis, and prothrombin time.	Efficacy Clinical resolution rate 7–21 days post-therapy: Rx1–90% Rx2–91% Bacteriological response rate: Rx1–91% Rx2–91% Safety Drug–related adverse events: Rx1–21% Rx2–19%

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Uncomplicated Skin and Skin Structure Infections

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Wise R, Andrews JM, Marshall G, Hartman G. Pharmacokinetics and inflammatory-fluid penetration of moxifloxacin following oral or intravenous administration. *Antimicrob Agents Chemother*. 1999;43:1508-1510.	Not given	8 healthy male volunteers	Each volunteer received 400 mg oral or IV moxifloxacin (administered over 1 h) in a random order, and 6 weeks later, received the agent by the other route	8 healthy male volunteers	Inclusion Healthy males between 26-41 years No history of serious illness, atopy, alcohol or drug abuse, or any acute illness in the 14 days prior to the start of the study Subjects had not received any prescribed or over-the-counter medication in the 14 days prior to the first dose	Efficacy Primary – Clinical response at 3-5 days post-Tx Secondary – Clinical response at 21-28 days post-Tx, bacteriological response 3-5 days and 21-28 days post-Tx, clinical and bacteriological response 3-5 days post-start of Tx Safety Clinical adverse reactions, standard lab assessments, and clinical variable	The mean maximum concentrations observed in plasma were 4.98 mg/mL after oral dosing and 5.09 mg/mL after IV dosing Mean maximum concentrations attained in inflammatory fluid were 2.62 and 3.23 mg/mL for oral and IV dosing, respectively Mean elimination half-lives from plasma were 8.32 and 8.17 h, respectively Overall penetration into the inflammatory fluid was 103.4% and 104.2% for oral and IV routes, respectively Over 24 h, 15% of the drug was recovered in the urine when administered by either route
Data on File. Study 0131/PH-27945. Schering Plough Corporation. Kenilworth, New Jersey.	April 26, 1997 (1st patient's 1st visit), to May 15, 1998 (last patient completed)	Phase III, comparative, multi-center, multi-national, prospective, parallel-group, randomized, controlled, double-blind	Rx1: moxifloxacin 400 mg PO QD for 5-14 days Rx2: cephalexin 500 mg t.i.d. with or without metronidazole 400 mg t.i.d. for 5-14 days	Efficacy Total–385 Rx1–191 Rx2–194 Safety Total–451 Rx1–227 Rx2–224	Inclusion Patients 18 years and above with acute (not present for more than 21 days), mild to moderate uncomplicated skin and soft tissue infection Two or more of following symptoms within 24 hours before enrollment in the study: fever > 38°C or chills, edema of skin/soft tissues, erythema of skin/soft tissues, purulent exudate, local pain or tenderness, local hyperthermia	Efficacy Primary – Clinical response at 1-7 days after end of therapy (EOT) (at visit 4) Secondary – Clinical and bacteriological responses on days 3-6 of therapy (at visit 2), 2-3 days later (at visit 3) and 8-21 days after EOT (at visit 5), also bacteriological response assessed 1-7 days after EOT (at visit 4) Safety Clinical adverse events, blood chemistry, hematology, urine sediment, urinalysis, and 12-lead ECG	Efficacy Clinical success rate at EOT: Rx1–92.7% Rx2–92.8% Clinical success rate at follow–up: Rx1–99.4% Rx2–98.2% Overall clinical success rate: Rx1–91.8% Rx2–91.0% Bacteriological response at EOT: Rx1–89.0% Rx2–93.8% Safety Drug related adverse events: Rx1–35.7% Rx2–25.9%

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Evidence Table Spreadsheet – Prospective Effectiveness Trials – Uncomplicated Skin and Skin Structure Infections

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Data on File. Study 0122/PH-27915. Schering-Plough Corporation. Kenilworth, New Jersey.	October 10, 1996 to May 6, 1997	Phase IIa, pilot, comparative, multi-center, parallel group, prospective, randomized, double-blind study	Rx1: moxifloxacin 200 mg PO QD for 5-14 days Rx2: moxifloxacin 400 mg PO QD for 5-14 days Rx3: cephalexin 500 mg t.i.d. for 5-14 days	Efficacy Total–69 Rx1–21 Rx2–22 Rx3-26 Safety Total–86 Rx1–30 Rx2–28 Rx3-28	Inclusion Patients 18 years and above with skin and soft tissue infection within 3 weeks of onset. Two or more of following symptoms within 24 hours before enrollment in the study: fever > 38°C or chills, edema of skin/soft tissues, erythema of skin/soft tissues, purulent exudate, local pain/ tenderness, and/or local hyperthermia	Efficacy Primary – Safety of Rx1, Rx2, and Rx3 in patients with mild to moderate uncomplicated skin and soft tissue infections Secondary – Clinical and microbiological efficacy of moxifloxacin and the clinical and microbiological response at the third day of treatment in all treatment groups. Safety Averse events and laboratory parameters	Efficacy Clinical success rate at EOT: Rx1–95.2% Rx2–100% Rx3-88.5% Bacteriological response at EOT: Rx1–72% Rx2–80% Rx3-80% Safety Drug related adverse events: Rx1–27% Rx2–50% Rx3-36%
Data on File. Study 300046/PH-32163. Schering Plough Corporation. Kenilworth, New Jersey.	April 24, 2000 to March 21, 2001 (1st patient's enrollment to last patient's completion)	Phase III, non-comparative, open label study	Rx1: moxifloxacin 400 mg PO QD for 7 days	Efficacy Rx1–147 Safety Rx1–159	Inclusion Male and female outpatients aged 20 years or older with bacterial skin and skin structure infections (including superficial skin infections, deep skin infections, and chronic pyoderma.	Efficacy Primary – Overall clinical efficacy assessed at the end of treatment Secondary – Bacteriological response at the end of treatment, clinical response as determined on day 5 and at the end of treatment. Safety Physical examination findings, adverse events, and laboratory tests including hematology, blood chemistry, and urinalysis.	Efficacy Overall clinical efficacy: Rx1–72.8% Bacteriological response rate: Rx1–85.3% Safety Drug–related adverse events: Rx1–25.8%

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Evidence Table Spreadsheet – Pivotal Safety and Efficacy Trials – Complicated Skin and Skin Structure Infections

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Data on File. Study 100273/MRR-00082. Schering Plough Corporation. Kenilworth, New Jersey.	December 12, 2000 to July 20, 2003 (1st patient's 1st visit to last patient's last visit)	Prospective, active-control, randomized, double-blind, multi-center	Rx1: IV/PO moxifloxacin 400 mg QD Rx2: IV piperacillin/ tazobactam 3.0 g/ 0.375 g Q6H followed by PO amoxicillin/ clavulanic acid suspension 800 mg Q12H IV treatment was administered for a minimum of 3 days and combined IV/PO treatment duration was 7 to 14 days.	Efficacy Total–367 Rx1–180 Rx2–187 Safety Total–601 Rx1–298 Rx2–303	Inclusion Male and female patients aged 18 years or older who were hospitalized with a diagnosis of complicated skin and skin structure infections requiring initial inpatient IV antimicrobial therapy.	Efficacy Primary – Clinical response at test of cure (TOC), 10-42 days after the last dose of st udy drug Secondary – Bacteriological success at the TOC, clinical and bacteriological response on the day of IV to PO switch or on treatment day 3-5 (if the day of switch was other than day 3, 4, or 5), mortality attributed to cSSSI at the TOC, days of hospitalization, days of hospitalization postoperatively (if applicable), and days of IV therapy Safety Monitoring for adverse events, laboratory tests, and ECG	Efficacy Clinical cure rate at TOC: Rx1–79.4% Rx2–81.8% Bacteriological response at TOC: Rx1–77.3% Rx2–81.4% Safety Drug related adverse events: Rx1–31.2% Rx2–30.0%
Data on File. Study 10279/MRR-00133. Schering Plough Corporation. Kenilworth, New Jersey.	April 03, 2001 to April 08, 2002 (1st patient's 1st visit to last patient's last visit)	Prospective, randomized, non-blinded, comparative with parallel group, multi-center and multi-national	Rx1: IV/PO moxifloxacin 400 mg q.d. Rx2: IV amoxicillin/ clavulanate* 1.0 g/200 mg TID followed by PO amoxicillin/ clavulanate 500 mg/125 mg TID IV treatment was administered for a minimum of 3 days and combined IV/PO treatment duration was 7 to 21 days.	Efficacy Total–632 Rx1–315 Rx2–317 Safety Total–803 Rx1–406 Rx2–397	Inclusion Male and female patients aged 18 years or older who presented with complicated skin and skin structure infection (cSSSI) of <21 days duration and how had only one site of skin and skin structure infection and required systemic antimicrobial treatment.	Efficacy Primary – Clinical response at day 14 to 28 after the end of treatment (TOC). Secondary – Clinical and bacteriological response on day 3 of treatment, bacteriological response at TOC, incidence of sepsis, incidence of nosocomial infections in relation to length of hospitalization, number of days of hospitalization in both t reatment regimens, major healthcare resources used from day 1 to days 14 to 28 after the end of study treatment, and clinical response at TOC for the individual diagnosis. Safety Based on physical examinations, laboratory tests (hematology, clinical chemistry, urinalysis, blood gases), and the reporting of adverse events.	Efficacy Clinical success rate at TOC: Rx1–80.6% Rx2–84.5% Bacteriological response rate: Rx1–76.0% Rx2–81.4% Safety Drug–related adverse events: Rx1–18% Rx2–16%

* IV amoxicillin clavulanate is not FDA approved.

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Evidence Table Spreadsheet – Prospective Effectiveness Trials – Community Acquired Pneumonia

Title/Citation	Study dates	Design	Treatments	Sample size	Inclusion/exclusion criteria	Endpoints	Results
Landen H and Bauer T. Efficacy, onset of action and tolerability of moxifloxacin in patients with community-acquired pneumonia. *Clin Drug Invest* 2001;21(12)	September 13, 1999 to March 31, 2001	Postmarketing surveillance study	Moxifloxacin 400 mg QD for up to 10 days	Total–2188	Inclusion Patients admitted to the hospital with CAP who had been prescribed moxifloxacin as the most appropriate therapy. Exclusion Patients suffering hospital acquired pneumonia	Efficacy Patients followed over entire course of treatment as well as post-treatment until discharge. Nine symptoms were assessed and recorded each day of treatment Safety The onset, nature, and duration of all adverse events reported during the study were recorded irrespective of causal relationship	Efficacy After 5 days of treatment almost 90% of patients showed improvement with 50% of patients symptom-free. 87% of patients were symptom-free after 10 days. At the conclusion of observation period, 93.4% of patients were cured or clinically improved Safety 4.8% of patients reported AE, and drug–related AEs occurred in 2.7% of patients Overall tolerability of moxifloxacin was rated as "very good" or "good" by 96% of physicians

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

2.2 Clinical and Disease Management Intervention Strategies

There are currently no Avelox studies or reports available that evaluate the impact of the product as part of a disease or care management intervention strategy. However, there is significant clinical trial data (please see Section 2.1 above) to show that Avelox is safe and effective in treating community-acquired pneumonia, acute sinusitis, acute exacerbations of chronic bronchitis, and skin and skin structure infections.

2.3 Economic Evaluation Supporting Data

Two summaries of the following studies are contained in this subsection:

- Drummond MF, Becker DL, Hux M, et al. An economic evaluation of sequential IV/PO moxifloxacin therapy compared to i.v./po co-amoxiclav with or without clarithromycin in the treatment of community-acquired pneumonia. *Chest*. 2003;124(2):526-535.

- Coughlin CM, Nelson M, Merchant S, et al. Costs of broad spectrum antibiotics use for acute sinusitis, chronic bronchitis, and pneumonia in a managed care population. *Manage Care Interface*. 2003: 34-40, 55.

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Citation: Drummond MF, Becker DL, Hux M, et al. An economic evaluation of sequential i.v./po moxifloxacin therapy compared to i.v./po co-amoxiclav with or without clarithromycin in the treatment of community-acquired pneumonia. *Chest.* 2003;124(2):526-535.

Location	Start Date & Duration	Trial Design	Inclusion Criteria	Exclusion Criteria
65 centers in 10 countries	February 1999 to May 2000	Multi-national, multi-center, randomized, open-label, phase III clinical trial	Adult patients newly hospitalized with radiologic evidence of community-acquired pneumonia (CAP) and requiring initial parenteral therapy	Exclusion criteria: presence of coexisting disease considered likely to affect the outcome of study; a rapidly fatal underlying disease; known prolongation of the QT interval or use of class IA or class III antiarrhythmics; known hypersensitivity to fluoroquinolones, ß-lactams, or macrolides; aspiration pneumonia; and pre-treatment with systemic antibacterial agents for > 24 hours prior to enrollment in study

Sample Characteristics – 622 Study Patients

	Moxifloxacin	AMC ± CLA[†]
Diagnosed with severe CAP *	> 50%	> 50%
Mean age	55.2	55.9
Sex – male	64.1%	64.5%
Preexisting bronchio-pulmonary disease	28%	29%
History of smoking	59%	61%

*According to the 1993 American Thoracic Society criteria.
[†]60% of patients were treated with both co-amoxiclav (AMC) and clarithromycin (CLA).

Treatment and Dosage Regimens

Patients randomized into one of 2 treatment groups (min. of 7 days and max. of 14 days):

- **Group 1 (moxifloxacin):** 400 mg IV q.d. for 3 days (min.) then switch to 400 mg p.o. q.d. at discretion of investigator
- **Group 2 (co-amoxiclav):** 1.2 g IV t.i.d. for 3 days (min.) then switch to 625 mg p.o. t.i.d.

Patients in group 2: clarithromycin 500 mg b.i.d. either IV or p.o. starting on the 1st day of Tx at discretion of investigator

Criteria for Evaluation

Efficacy

- **Primary** – Clinical response at 5 to 7 days after the termination of the study drug treatment (i.e., test-of-cure [TOC] visit)
- **Secondary** – Collect resource utilization data associated with CAP for use in economic evaluation

Safety

Clinical adverse events

Base Cost and Sensitivity Analysis Results for Germany and France

Germany (in euros, €)			France (in euros, €)			Effectiveness (%)	
Variables	Mean Cost per Patient	Difference (95% CI)	Variables	Mean Cost per Patient	Difference (95% CI)	Patients Cured	Difference (95% CI)
Base-case analysis			**Base-case analysis**				
AMC ± CLA	2244		AMC ± CLA	4071		75.4	
Moxifloxacin	1978	–266 (–549 to 17)	Moxifloxacin	3690	–381 (–835 to 73)	80.7	5.3 (–1.2 to 11.8)
Cost of hospitalization			**Cost of hospitalization using minimum value**				
AMC ± CLA	3442		AMC ± CLA	2246		75.4	
Moxifloxacin	3001	–441	Moxifloxacin	2117	–129	80.7	5.3
Cost of erythromycin IV substituted for clarithromycin IV			**Cost of hospitalization using maximum value**				
AMC ± CLA	2237		AMC ± CLA	8090		75.4	
Moxifloxacin	1978	–259	Moxifloxacin	7288	–802	80.7	5.3

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Most Common Adverse Events

	Moxifloxacin	AMC ± CLA
Abnormal liver function tests	7.3%	5.9%
Diarrhea	7.0%	5.3%
Nausea	3.3%	3.7%
Rate of clinical cure at TOC visit	80.7%	75.4%

Difference of 5.3%, 95% CI (1.2%, 11.8%)

Results

- Compared with AMC ± CLA, treatment with moxifloxacin resulted in 5.3% more patients achieving clinical cure 5-7 days after therapy (95% CI: 1.2%, 11.8%), increased speed of response, and achieving a reduction in hospital stay by 0.81 days within the 21-day timeframe. Treatment with moxifloxacin resulted in savings of €266 (11%) and €381 (9%) for Germany and France, respectively, primarily due to the shorter length of hospital stay

Cost comparisons are not intended to compare efficacy.

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Citation: Coughlin CM, Nelson M, Merchant S, et al. Costs of broad spectrum antibiotics use for acute sinusitis, chronic bronchitis, and pneumonia in a managed care population. *Manage Care Interface* 2003:34-40, 55.

Study Design	Analysis Period	Inclusion/Exclusion Criteria
Retrospective database analysis	Claims data from 6 discounted, fee-for-service, independent practice association model health plans between April 1, 2000, and March 31, 2001	**Inclusion** • Prescription filled for at least 1 of the study drugs during the analysis period • Continuous plan enrollment between October 1, 1999, and March 31, 2001 • ≥ 18 years of age as of January 1, 2000, and insurance coverage with a drug benefit **Exclusion** • More than 1 antibiotic prescription filled on the same date as index drug

Sample Characteristics – No. of Patients

	18-64 y	65+ y	Total (%)
Females	79,238	2249	81,487(57)
Males	58,879	2347	61,226(43)
Total (%)	138,117 (96.8)	4596 (3.2)	142,713

- Total plan population approximately 2,000,000
- Sample mean age = 42.4 years
- A slightly higher proportion of subjects 65+ years were prescribed gatifloxacin, levofloxacin, and moxifloxacin compared with other 3 study drugs

Study Drugs*

Azithromycin, amoxicillin-clavulanate, clarithromycin, gatifloxacin, and moxifloxacin were each compared with levofloxacin

*Includes drugs from 1st, 2nd, 3rd tiers

Treatment Classification

- **Index drug:** defined as the 1st study drug prescription claim filled during analysis period
- Index drug date defined as the date on which the index drug was filled
- Index drug was first-line therapy (N = 105,501) if there were no antibiotic claims 90 days prior to index drug date
- Re-treatment defined as the occurrence of a subsequent antibiotic claim within 30 days after the completion of the index treatment

Distribution by Type of Index Drug

Index Rx	No. (%) of Subjects*†	No. (%) by Reason for Treatment		
		Acute Sinusitis	Chronic Bronchitis	Pneumonia
Amoxicillin/Clavulanate	27,526 (19)	6,384 (23)	130 (0.5)	358 (1)
Azithromycin	73,892 (52)	10,534 (14)	617 (0.8)	1,312 (1.8)
Clarithromycin	19,044 (13)	4,247 (22)	293 (1.5)	885 (4.6)
Gatifloxacin	2,936 (2)	713 (24)	58 (2)	199 (6.8)
Levofloxacin	17,545 (12)	2,545 (14)	292 (1.7)	1,209 (7)
Moxifloxacin	1,770 (1)	446 (25)	29 (1.6)	74 (4.2)
Total	142,713	24,869	1,419	4,037

*Includes patients with respiratory tract infections other than acute sinusitis, chronic bronchitis, and pneumonia.
†Includes patients on first- and second-line antibiotics.

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Disease Conditions Used to Define Treatment			
Disease Condition	**Number of Subjects (%)**	**Number (%) First Line**	**Number (%) of Those with First Line Who Experienced Re-treatment**
Acute sinusitis	24,869 (17.4)	18,561 (75)	3,604 (19)
Pneumonia	4,037 (2.8)	3,018 (75)	807 (27)
Chronic bronchitis	1,419 (1)	994 (70)	249 (25)
All other conditions	75,312 (52.8)	55,879 (74)	10,263 (18)
Unknown/none	37,646 (26.4)	27,423 (73)	4,667 (17)

Regression Model Results Compared To Levofloxacin†						
Variable	**Acute Sinusitis** N=18,484 (77) †		**Chronic Bronchitis** N=955 (39) †		**Pneumonia** N=2,990 (28) †	
	N (%)	**% Difference**	**N (%)**	**% Differencœ**	**N (%)**	**% Difference**
Age		0.11?		0.7?*		0.24?*
Male		1.2?		14?*		2.1?
Re-treatment		62?*		56?*		58?*
Moxifloxacin	321 (1.7)	8?*	23 (2.4)	32?*	57 (1.9)	44?*
Gatifloxacin	469 (2.5)	13?*	39 (4.1)	12?	157 (5.3)	36?*
Azithromycin	8,032 (43.5)	32?*	452 (47.3)	44?*	973 (32.5)	45?*
Clarithromycin	3,170 (17.1)	6?*	196 (20.5)	29?*	675 (22.6)	40?*
Amoxicillin/clavulanate	4,774 (25.8)	**71***	**81** (8.5)	251*	264 8.8	25?*
Levofloxacin	1,718 (9.3)	Reference	164 (17.2)	Reference	864 (28.8)	Reference

*$P < 0.05$.

†Subjects greater than 3 standard deviations from the mean were omitted

??= costs relative to levofloxacin.

Cost comparisons are not intended to compare efficacy.

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Section 3.
Economic Burden of Disease

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

3. Economic Burden of Disease

Summary

Community-Acquired Pneumonia (CAP):

CAP remains a common and serious illness. In the United States, CAP is the sixth leading cause of death and the most common infectious cause (Bartlett et al, 2000; Niederman et al, 2001). More than 80% of cases of CAP are managed in the community, where the mortality rate is around 1%. Among those approximately 500,000 patients admitted to the hospital each year, 10%-14% will die, with the mortality rate rising to 30%-40% for those requiring intensive care (Bartlett et al, 2000). Approximately 10% of CAP cases are severe enough to require intensive care and/or mechanical ventilation. The aging population, increased prevalence of comorbid illnesses, infection with human immunodeficiency virus, and increasing microbial resistance probably all have contributed to maintaining the high mortality rate despite advances in medical care. Annual CAP patient treatment costs were $9.7 billion in 1994; 92% of these costs were associated with inpatient therapy. There is substantial disparity in cost between an episode of inpatient and outpatient therapy ($7,517 versus $264) (Lave et al, 1999).

Acute Bacterial Sinusitis (ABS):

Nearly 20 million cases of acute bacterial rhinosinusitis (ABS) are managed annually, at an estimated cost of $3.5 billion per year in the United States (Anon et al, 2004). Additionally, many persons experience symptoms of sinusitis but do not seek medical attention, indicating the true burden of sinusitis might be even higher than these estimates. Sinusitis is the fifth most common diagnosis for which antibiotics are prescribed. Sinusitis accounted for 21% of all adult antibiotic prescriptions written in 2002 (Anon et al, 2004).

Acute Bacterial Exacerbations of Chronic Bronchitis (ABECB):

Despite public education about the dangers of smoking, COPD continues to be a major medical problem and is now the fourth leading cause of death in the United States (NHLBI, 2003). The cost of COPD to the nation in 2002 was estimated to be $32.1 billion (NHLBI, 2003). Acute bronchitis and acute exacerbations of COPD are among the most common illnesses encountered by family physicians and account for more than 16 million physician visits annually (McCrory et al, 2001). A problem common to all patients with COPD, regardless of disease severity, is acute exacerbations of chronic bronchitis (ABECB), with some or all of the cardinal symptoms of increased dyspnea, increased sputum volume, and increased sputum purulence (McCrory et al, 2001). Acute exacerbations that require hospitalization are associated with an inpatient mortality rate of 3 to 4%. Patients that do require hospitalization are typically readmitted an additional time within 6 months of their previous hospital admission (McCrory et al, 2001).

Uncomplicated Skin and Skin Structure Infections:

Infections of the skin and soft tissues are among the most common types of acute infectious illness encountered in physician practices. In fact, bacterial skin infection is the 28th most common diagnosis in the hospital setting (Stulberg et al, 2002).

Health Outcomes

CAP:

The specific factors that are associated with improved patient outcomes in CAP include time to antibiotic administration, blood culture collection, and appropriate empirical antibiotic selection. The normal resolution of pneumonia is not easily defined and may vary depending upon the underlying cause, as well as the host. Patients typically note subjective improvement within 3 to 5 days of treatment. More specific clinical criteria for resolution include improvement in fever, rigors, sweats, dyspnea, sputum production, and color or respiratory secretions (Bartlett et al, 2000). However, most studies on the natural history of pneumonia have focused upon the resolution of chest radiographic abnormalities, with "slow resolution" often being defined as the persistence of radiographic abnormalities for > 1 month in a clinically improved host (Arancibia et al, 2000). Slow or incomplete resolution of pneumonia despite treatment is a common clinical problem (Arancibia et al, 2000).

ABS:

For acute bacterial sinusitis, studies have shown that 80% to 90% of patients experience symptomatic and bacteriologic improvement within 7 to 14 days of antibiotic therapy (Fagnan 1998). In those patients with inadequate or failed responses to treatment, complications may include development of sepsis, intracranial venous thrombosis, meningitis, periorbital/orbital cellulitis or abscess, or intracranial abscess (The Alberta Medical Association, 2001).

ABECB:

Resolution of symptoms of ABECB include decreased volume and clearing color of sputum, improved cough, decreased dyspnea, decreased chest tightness and wheezing, and decreased fever (Pauwels et al, 2001). Antibiotic therapy is administered to patients with ABECB to improve peak flow volume in patients with dyspnea (Ball, 1995). The normal course of an ABECB will vary depending on the severity of the underlying disease, and while patients may improve without antimicrobial therapy, some untreated patients will require hospitalization subsequent to developing pneumonia and respiratory insufficiency (Chodosh et al, 2000).

USSSI:

The expected outcomes of therapy for uSSSI include complete resolution of redness, swelling, pain. Systemic improvements from antimicrobial treatment include resolution of fever and elevated white blood cell counts (O'Dell, 1998.)

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Economic Model

The purpose of the budget impact model is to understand the impact of changes in market distribution for fluoroquinolones (FQ). This information will allow decision makers to compare the amount spent on fluoroquinolone agents with varying FQ market shares. Two base-case scenarios are provided, including data for a typical health plan.

The model was developed using Microsoft Excel. The model calculates drug costs in the fluoroquinolone market for seven different fluoroquinolones (Avelox®, Levaquin® (levofloxacin), Tequin® (gatifloxacin), Cipro® XR (ciprofloxacin extended release tablets), Cipro® (ciprofloxacin HCl), single generic ciprofloxacin, and generic ciprofloxacin (Teva Pharmaceuticals) based on the average wholesale price (AWP*), dispensing fee per prescription, patient co-pay, network discount, manufacturer's rebate, and population distributions associated with each drug.

The following parameters are used in the model:

- The total number of members in the plan (the default is 1,000,000).
- The average wholesale price (AWP), dispensing fee per prescription, patient copay, network discount, and manufacturer's rebate associated with each drug (Table 1).
- An economic evaluation based on a hypothetical distribution of patients according to the dosage form of each drug, and current and future market share of FQs (Tables 2, 3, and 4).
- An economic evaluation of the impact of switching formulary tier status for Levaquin and Avelox in a scenario where 2nd tier Levaquin is switched to 3rd tier status, and 3rd tier Avelox is switched to 2nd tier status (Tables 5 and 6).

* Schering Corporation does not declare an AWP.

Cost comparisons are not intended to compare efficacy.

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Table 1. Cost of Fluoroquinolone Prescriptions: *Costs and Rebates (April 2005)*

Drug	Strength	Average # of Days per Prescription *	AWP Cost Per Day of Therapy †	AWP per Prescription ‡	Dispensing Fee per Prescription †	Patient Copayment†	Network Discount †	Mfg.'s Rebate†	Current Cost per Prescription to Health Plan§
		STEP 1	STEP 2		STEP 3	STEP 4	STEP 5	STEP 6	
LEVAQUIN® ǁ (levofloxacin) *Once Daily Dosing*	250 mg	8	$9.80	$78.40	$2.00	$40.00	15%	0%	$28.64
	500 mg	9.3	$11.24	$104.53	$2.00	$40.00	15%	0%	$50.85
	750 mg	7.5	$21.05	$157.88	$2.00	$40.00	15%	0%	$96.19
AVELOX® (moxifloxacin HCl) *Once Daily Dosing*	400 mg	9	$10.70	$96.30	$2.00	$22.00	15%	28%	$40.28
TEQUIN® (gatifloxacin) *Once Daily Dosing*	200 mg	8	$9.85	$78.80	$2.00	$40.00	15%	0%	$28.98
	400 mg	8.6	$9.85	$84.71	$2.00	$40.00	15%	0%	$34.00
CIPRO® XR (ciprofloxacin* extended release tablets) *Once Daily Dosing*	500 mg	6.5	$8.66	$56.29	$2.00	$40.00	15%	0%	$9.85
	1 gram	8.9	$9.86	$87.75	$2.00	$40.00	15%	0%	$36.59
CIPRO® (ciprofloxacin HCL) tablets *Twice Daily Dosing*	250 mg	7.6	$4.90	$37.24	$2.00	$0.00	15%	0%	$33.65
	500 mg	8.7	$5.74	$49.94	$2.00	$0.00	15%	0%	$44.45
	750 mg	11.4	$6.02	$68.63	$2.00	$0.00	15%	0%	$60.33
Single Generic Cipro *Twice Daily Dosing+B18*	250 mg	7.3	$4.59	$33.51	$2.00	$0.00	15%	0%	$30.48
	500 mg	8.2	$5.38	$44.12	$2.00	$0.00	15%	0%	$39.50
	750 mg	10.8	$12.53	$135.32	$2.00	$0.00	15%	0%	$117.03
Generic Cipro (Teva) *Twice Daily Dosing*	250 mg	7.3	$4.59	$33.51	$2.00	$0.00	15%	0%	$30.48
	500 mg	8.4	$5.38	$45.19	$2.00	$0.00	15%	0%	$40.41
	750 mg	10.8	$12.53	$135.32	$2.00	$0.00	15%	0%	$117.03

* IMS health, National Prescriptions Audit (NPA), June 18, 2004

† Default value only, may be changed to reflect specific plan, ± Red Book, April 2005

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Table 2. Percentage of Patients on Each Product (hypothetical distribution)

Number of Members in Plan:			1,000,000		
PROJECTED UTILIZATION AND COSTS					
Drug Name		BaselineCost per Prescription ($) to Health Plan	Projected Market Share (% of Total Rxs)†	Projected Annual Prescriptions*	Projected Annual Cost ($)†
			STEP 15		
LEVAQUIN® (levofloxacin) *Once Daily Dosing*	250 mg	$28.64	2%	4148	$118,799
	500 mg	$50.85	13%	22512	$1,144,804
	750 mg	$96.19	1%	1037	$99,753
AVELOX® (moxifloxacin HCl) *Once Daily Dosing*	400 mg	$40.28	18%	30467	$1,227,311
			0%		
TEQUIN® (gatifloxacin) *Once Daily Dosing*	200 mg	$28.98	0%	654	$18,953
	400 mg	$34.00	3%	5889	$200,247
CIPRO® XR (ciprofloxacin* extended release tablets) *Once Daily Dosing*	500 mg	$9.85	1%	1484	$14,612
	1 gram	$36.59	1%	2225	$81,415
CIPRO® (ciprofloxacin HCL) tablets *Twice Daily Dosing*	250 mg	$33.65	8%	13762	$463,146
	500 mg	$44.45	33%	55046	$2,446,646
	750 mg	$60.33	14%	22936	$1,383,816
Single Generic Cipro *Twice Daily Dosing+B18*	250 mg	$30.48	1%	1365	$41,606
	500 mg	$39.50	3%	5459	$215,623
	750 mg	$117.03	1%	2275	$266,233
Generic Cipro (Teva) *Twice Daily Dosing*	250 mg	$30.48	0%	0	$0
	500 mg	$40.41	0%	0	$0
	750 mg	$117.03	0%	0	$0
Total			**100%**	**169259**	**$7,722,964**

† Default value only, may be changed to reflect specific plan

Key Assumptions

The example presented here is based on product information and data obtained from publicly available sources. It is assumed that a typical health plan has 1,000,000 lives. The model results are generated once the required information is entered and are dependent upon the assumptions of data entry. The key cost savings in the model is derived from the difference in AWP, and possible differences in patient copay and manufacturer's rebate associated with each drug.

Model Results

The total cost per prescription for each drug is calculated by using the following formula:

Cost = [AWP per prescription + dispensing fee – (network discount ´ AWP per prescription) – copay - (manufacturer's rebate ´ 0.8 ´ AWP per prescription)]

In scenario one, an economic evaluation based on a hypothetical distribution of patients according to the dosage form of each drug, and current and future market share of FQs is analyzed.

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

The percentage of patients on each product (as shown in Tables 3 and 4) demonstrates the impact of a change in the market distribution. From an existing 20% market share by Levaquin (2.5%, 17.4%, and 0.6% for 250-, 500-, and 750-mg doses, respectively), the hypothetical scenario (Future Population Distribution) indicates 16% market share for Levaquin (2%, 13%, and 1% for 250-, 500-, and 750-mg doses, respectively) and a 18% market share for Avelox® (400 mg).

The economic impact of change in market share amongst FQs in a typical plan is demonstrated in Tables 3 and 4.

Table 3. Current Utilization and Costs

Number of Members in Plan:			1,000,000		
CURRENT UTILIZATION AND COSTS					
Drug Name		**Current Cost per Prescription ($) to Health Plan**	**Current Annual Prescriptions (2004)**	**Current Market Share (% of Total Rxs)†**	**Current Annual Cost ($)†**
			STEP 14		
LEVAQUIN® (levofloxacin) *Once Daily Dosing*	250 mg	$28.64	4148	2.5%	$118,799
	500 mg	$50.85	29379	17.4%	$1,493,987
	750 mg	$96.19	1037	0.6%	$99,753
AVELOX® (moxifloxacin HCl) *Once Daily Dosing*	400 mg	$40.28	23600	13.9%	$950,698
				0.0%	
TEQUIN® (gatifloxacin) *Once Daily Dosing*	200 mg	$28.98	654	0.4%	$18,953
	400 mg	$34.00	5889	3.5%	$200,247
CIPRO® XR (ciprofloxacin* extended release tablets) *Once Daily Dosing*	500 mg	$9.85	1484	0.9%	$14,612
	1 gram	$36.59	2225	1.3%	$81,415
CIPRO® (ciprofloxacin HCL) tablets *Twice Daily Dosing*	250 mg	$33.65	13762	8.1%	$463,146
	500 mg	$44.45	55046	32.5%	$2,446,646
	750 mg	$60.33	22936	13.6%	$1,383,816
Single Generic Cipro *Twice Daily Dosing+B18*	250 mg	$30.48	1365	0.8%	$41,606
	500 mg	$39.50	5459	3.2%	$215,623
	750 mg	$117.03	2275	1.3%	$266,233
Generic Cipro (Teva) *Twice Daily Dosing*	250 mg	$30.48	0	0.0%	$0
	500 mg	$40.41	0	0.0%	$0
	750 mg	$117.03	0	0.0%	$0
Total			**169259**	**100%**	**$7,795,533**

*Current annual cost = current annual prescriptions × cost per prescription to health plan.

† Default value only, may be changed to reflect specific plan

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Table 4. Future Utilization and Costs

Number of Members in Plan:		1,000,000			
PROJECTED UTILIZATION AND COSTS					
Drug Name		BaselineCost per Prescription ($) to Health Plan	Projected Market Share (% of Total Rxs)	Projected Annual Prescriptions†	Projected Annual Cost ($)†
			STEP 15		
LEVAQUIN® (levofloxacin) *Once Daily Dosing*	250 mg	$28.64	2%	4148	$118,799
	500 mg	$50.85	13%	22512	$1,144,804
	750 mg	$96.19	1%	1037	$99,753
AVELOX® (moxifloxacin HCl) *Once Daily Dosing*	400 mg	$40.28	18%	30467	$1,227,311
			0%		
TEQUIN® (gatifloxacin) *Once Daily Dosing*	200 mg	$28.98	0%	654	$18,953
	400 mg	$34.00	3%	5889	$200,247
CIPRO® XR (ciprofloxacin* extended release tablets) *Once Daily Dosing*	500 mg	$9.85	1%	1484	$14,612
	1 gram	$36.59	1%	2225	$81,415
CIPRO® (ciprofloxacin HCL) tablets *Twice Daily Dosing*	250 mg	$33.65	8%	13762	$463,146
	500 mg	$44.45	33%	55046	$2,446,646
	750 mg	$60.33	14%	22936	$1,383,816
Single Generic Cipro *Twice Daily Dosing+B18*	250 mg	$30.48	1%	1365	$41,606
	500 mg	$39.50	3%	5459	$215,623
	750 mg	$117.03	1%	2275	$266,233
Generic Cipro (Teva) *Twice Daily Dosing*	250 mg	$30.48	0%	0	$0
	500 mg	$40.41	0%	0	$0
	750 mg	$117.03	0%	0	$0
Total			**100%**	**169259**	**$7,722,964**

†Projected annual cost = projected annual prescriptions × projected cost per prescription to the health plan.

† Default value only, may be changed to reflect specific plan

As a result of the shift in market scenario, there is a decrease in pharmacy expenditures from $7,795,533 to $7,722,964, resulting in a savings of $72,569, which is a 0.93% decrease over the current budget.

In scenario two, an economic evaluation of the impact of switching formulary tier status is evaluated. Specifically, 2nd tier Levaquin is switched to 3rd tier status, and 3rd tier Avelox is switched to 2nd tier status (Tables 5 and 6).

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

Table 5. Current 2nd Tier Levaquin (co-pay $22) vs 3rd Tier Avelox (co-pay $40)

Drug	Strength	Average # of Days per Prescription *	AWP Cost Per Day of Therapy†	AWP per Prescription ‡	Dispensing Fee per Prescription †	Patient Copayment †	Network Discount †	Mfg.'s Rebate†	Current Cost per Prescription to Health Plan§
		STEP 1	STEP 2		STEP 3	STEP 4	STEP 5	STEP 6	
LEVAQUIN® II (levofloxacin) *Once Daily Dosing*	250 mg	8	$9.80	$78.40	$2.00	$22.00	15%	0%	$46.64
	500 mg	9.3	$11.24	$104.53	$2.00	$22.00	15%	0%	$68.85
	750 mg	7.5	$21.05	$157.88	$2.00	$22.00	15%	0%	$114.19
AVELOX® (moxifloxacin HCl *Once Daily Dosing*	400 mg	9	$10.70	$96.30	$2.00	$40.00	15%	28%	$22.28
TEQUIN® (gatifloxacin) *Once Daily Dosing*	200 mg	8	$9.85	$78.80	$2.00	$40.00	15%	0%	$28.98
	400 mg	8.6	$9.85	$84.71	$2.00	$40.00	15%	0%	$34.00
CIPRO® XR (ciprofloxacin* extended release tablets) *Once Daily Dosing*	500 mg	6.5	$8.66	$56.29	$2.00	$40.00	15%	0%	$9.85
	1 gram	8.9	$9.86	$87.75	$2.00	$40.00	15%	0%	$36.59
CIPRO® (ciprofloxacin HCL) tablets *Twice Daily Dosing*	250 mg	7.6	$4.90	$37.24	$2.00	$0.00	15%	0%	$33.65
	500 mg	8.7	$5.74	$49.94	$2.00	$0.00	15%	0%	$44.45
	750 mg	11.4	$6.02	$68.63	$2.00	$0.00	15%	0%	$60.33
Single GenericCipro *Twice Daily Dosing+B18*	250 mg	7.3	$4.59	$33.51	$2.00	$0.00	15%	0%	$30.48
	500 mg	8.2	$5.38	$44.12	$2.00	$0.00	15%	0%	$39.50
	750 mg	10.8	$12.53	$135.32	$2.00	$0.00	15%	0%	$117.03
GenericCipro (Teva) *Twice Daily Dosing*	250 mg	7.3	$4.59	$33.51	$2.00	$0.00	15%	0%	$30.48
	500 mg	8.4	$5.38	$45.19	$2.00	$0.00	15%	0%	$40.41
	750 mg	10.8	$12.53	$135.32	$2.00	$0.00	15%	0%	$117.03

* IMS health, National Prescriptions Audit (NPA), June 18, 2004

† Default value only, may be changed to reflect specific plan

Table 6. Projected 3rd Tier Levaquin (co-pay $40) vs 2rd Tier Avleox (co-pay $22)

Drug	Strength	Average # of Days per Prescription *	AWP Cost Per Day of Therapy†	AWP per Prescription ‡	Dispensing Fee per Prescription †	Patient Copayment†	Network Discount†	Mfg.'s Rebate†	Projected Cost per Prescription to Health Plan§
		STEP 7	STEP 8		STEP 9	STEP 10	STEP 11	STEP 12	
LEVAQUIN® (levofloxacin) *Once Daily Dosing*	250 mg	8	$9.80	$78.40	$2.00	$40.00	15%	0%	$28.64
	500 mg	9.3	$11.24	$104.53	$2.00	$40.00	15%	0%	$50.85
	750 mg	7.5	$21.05	$157.88	$2.00	$40.00	15%	0%	$96.19
AVELOX® (moxifloxacin HCl) *Once Daily Dosing*	400 mg	9	$10.70	$96.30	$2.00	$22.00	15%	28%	$40.28
TEQUIN® (gatifloxacin) *Once Daily Dosing*	200 mg	8	$9.85	$78.80	$2.00	$40.00	15%	0%	$28.98
	400 mg	8.6	$9.85	$84.71	$2.00	$40.00	15%	0%	$34.00
CIPRO® XR (ciprofloxacin* extended release tablets) *Once Daily Dosing*	500 mg	6.5	$8.66	$56.29	$2.00	$40.00	15%	0%	$9.85
	1 gram	8.9	$9.86	$87.75	$2.00	$40.00	15%	0%	$36.59
CIPRO® (ciprofloxacin HCL) tablets *Twice Daily Dosing*	250 mg	7.6	$4.90	$37.24	$2.00	$0.00	15%	0%	$33.65
	500 mg	8.7	$5.74	$49.94	$2.00	$0.00	15%	0%	$44.45
	750 mg	11.4	$6.02	$68.63	$2.00	$0.00	15%	0%	$60.33
Single Generic Cipro *Twice Daily Dosing+B18*	250 mg	7.3	$4.59	$33.51	$2.00	$0.00	15%	0%	$30.48
	500 mg	8.2	$5.38	$44.12	$2.00	$0.00	15%	0%	$39.50
	750 mg	10.8	$12.53	$135.32	$2.00	$0.00	15%	0%	$117.03
Generic Cipro (Teva) *Twice Daily Dosing*	250 mg	7.3	$4.59	$33.51	$2.00	$0.00	15%	0%	$30.48
	500 mg	8.4	$5.38	$45.19	$2.00	$0.00	15%	0%	$40.41
	750 mg	10.8	$12.53	$135.32	$2.00	$0.00	15%	0%	$117.03

qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

* IMS health, National Prescriptions Audit (NPA), June 18, 2004

† Default value only, may be changed to reflect specific plan

As a result of the shift in tier status there is a decrease in pharmacy expenditures from $7,992,885 to $7,795,533, resulting in a savings of $197,352, which is a 2.47% decrease over the current budget.

This simulation tool allows for the exploration of different scenarios associated with the market share and cost drivers of fluoroquinolones. In the first example, we demonstrate how to explore a shift in market share. This is accomplished by adjusting the "Projected Utilization and Costs" tab. Increasing the Avelox market share by approximately 4% at the expense of Levaquin 500 mg market share resulted in a 1% decrease in the FQ budget.

We demonstrate in the second example how to explore a shift in drug tiering within a benefits plan. This is accomplished by changing the patient co-payment in the "Projected Costs and Rebates Tab" for the appropriate drugs. By reversing the patient co-payment amounts, so that Levaquin products have a patient co-payment of $40 and Avelox has a patient co-payment of $22, the budget impact is a savings of $197,352 or approximately 2.5% of the FQ budget.

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qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event

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qd=once daily; bid=twice daily; tid=thrice daily; po=orally; d=day; EOT=end of treatment; ITT=intent to treat; TOC=test of cure; PP=per protocol; AE=adverse event